55

Autoimmune CTDs

(Rheumatic diseases)

1-Lupus Erythematosus (LE)
2-Dermatomyositis (DM)
3-Systemic sclerosis (SSc)
4-Sjögren's syndrome (SS)
5-Mixed CTD (MCTD)
6-Raynaud's Phenomenon
7-Others: (*for MD*):
- A-Rheumatoid arthritis
- B-Juvenile Rheumatoid arthritis
- C-Adult-onset Still's disease
- D- Interstitial granulomatous dermatitis
- E-Relapsing polychondritis

8-Autoantibodies Encountered in Patients with Autoimmune Connective Tissue Diseases

By :
DR.Hany Abou-Elwafa
0104018946

Auto-immune connective tissue diseases (AI- CTDs)

Introduction and nomenclature:

The autoimmune connective tissue diseases (AI-CTDs) are a group of polygenic clinical disorders often having heterogeneous and overlapping clinical features; A hallmark of these disorders is the production of circulating autoantibodies (aAb) that have been identified by various immunochemical techniques.

They are called connective tissue diseases because all of them associated with pathological changes in collagen eg.;

*SSC:Associated with collagen hyalinization.

*LE and DM: Both show increased dermal mucin.

*Bullous SLE:Associated with autoantibodies against collagen VII.

The term 'Rheumatic diseases' can be used synonymously for AI-CTD. It should be noted that the older designation, 'collagen vascular diseases', is an obsolete terminology that should be avoided. Furthermore, the unqualified term 'connective tissue diseases' can cause confusion with genetic disorders that involve structural abnormalities of connective tissue, for example Ehlers– Danlos syndrome.

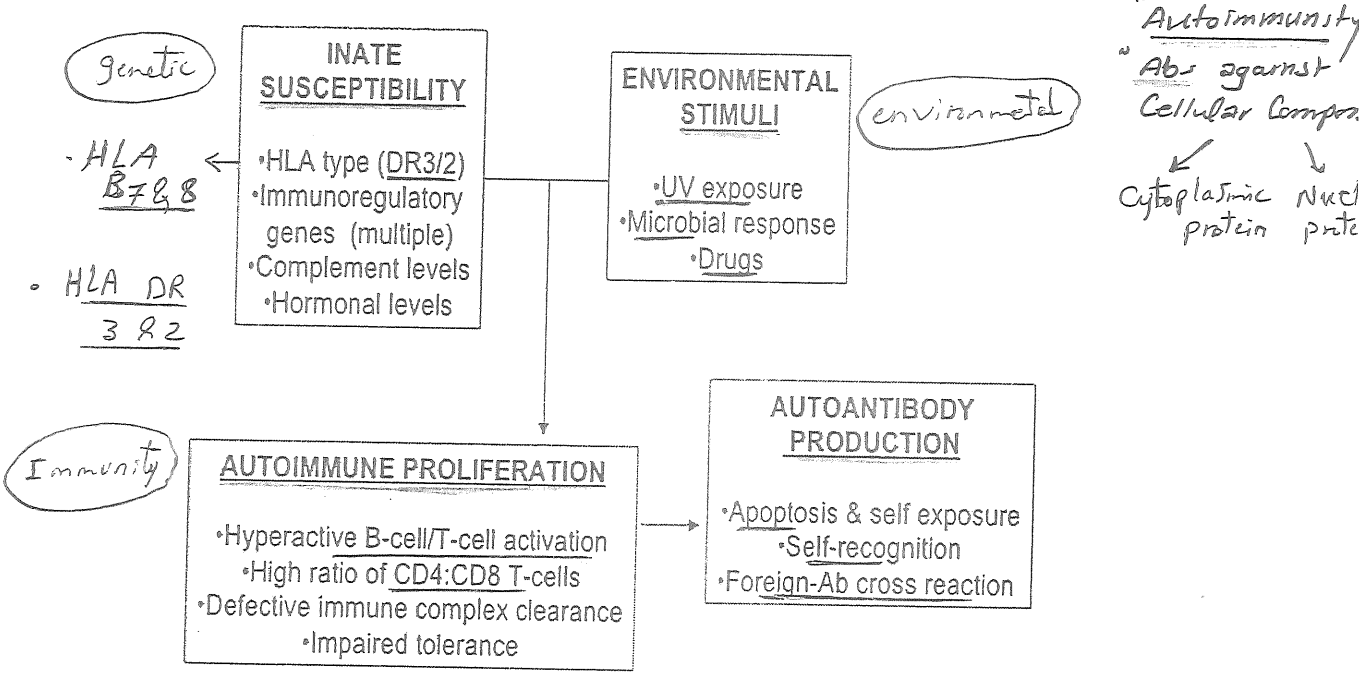
chronic idiopathic AI-CTDs ch' by formation of Auto-Abs against cytoplasmic & nuclear proteins & predominant skin affection

Lupus Erythematosus (LE)

Definition: chronic, idiopathic, AI-CTD with multisystem affection that prominently affects the skin. (ch' by formation of Auts. Abs)

NB: *Lupus means*: any skin disease in which the lesions are characteristically eroded.

Etiology and pathophysiology: uknown (multifactorial): Genetic + Environmental → Autoimmunity



"Abs against Cellular Compon.
Cytoplasmic protein
Nucl prote

In lupus erythematosus (LE), many genetic-susceptibility factors, environmental triggers, antigen-antibody responses, B-cell and T-cell interactions, and immune clearance processes interact to generate and perpetuate autoimmunity

- When LE affects The skin; This is Called Cutaneous LE (CLE).
- There are 3 Types of CLE Classified According to The degree of dis. progression (& Systemic affects):

- progress in (mś-ys) → 1. Chronic CLE (CCLE) = Discoid LE (DLE)
- Progress in few ws-ms → 2. Subacute CLE (SCLE).
- Progress in Few days → 3. Acute CLE (ACLE) = SLE. (LE ē Systemic organ involvem.)

NB. Gilliam & Sontheimer Classified the Cut. manifs of LE into:

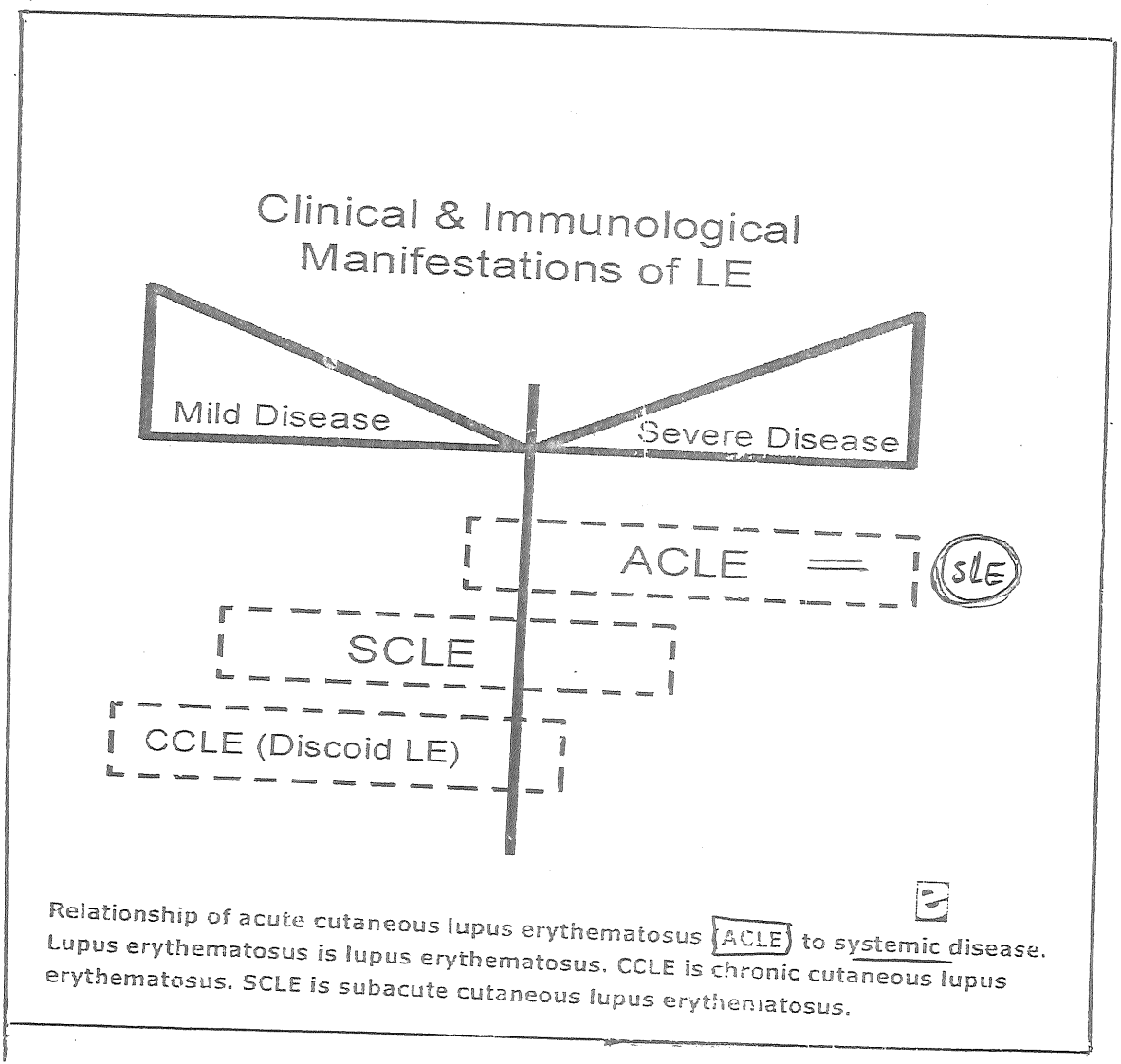
A. Specefic: DLE, SCLE & ACLE lesions.

B. Non ": ass. ē SLE.

Types of Cut. LE

(Cut. L.E spectrum)

	Chr. Cut. L.E (DLE)	Subacute Cut. LE (SCLE)	ACute Cut. L.E (ACLE = SLE)
• Dis. progression	• Ms - Ys	• Ws - mos	• days.
• M : F	• 1 : 2	• 1 : 3	• 1 : 9
• Cut. lesion	• Chronic Discoid plaques That Heal with (difiguring scars)	• less Chronic, annular or psoriasiform photosensitive Eruption That heal (out-scarring)	• Short lived, Severe Eruption usually Malar rash.
• Risk of systemic affects (SLE) development	• +	• ++	• (+++) (SLE)
• photosensitivity	• +	(+++)	• ++



Relationship of acute cutaneous lupus erythematosus (ACLE) to systemic disease. Lupus erythematosus is lupus erythematosus. CCLE is chronic cutaneous lupus erythematosus. SCLE is subacute cutaneous lupus erythematosus.

سؤال امتحان

DLE
(CCLE)

[illegible]
[illegible]
Emed . 2010
Fitz .
[illegible]

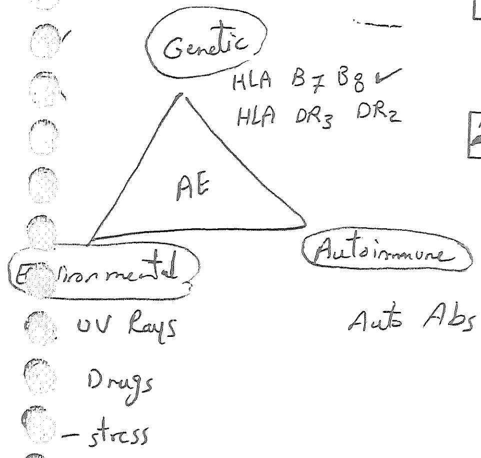
Def. Chr. Benign Cut. Pole of L.E Spectrum That Ch. By ← [illegible]

· **Epidemiology**:
- Age: any but usually **20-40 Y.** (Mean 38)
- Sex: M:F = **1:2**
- Race: any but more in (African).
- HLA-B7 & B8

· **Aetiology**: → unknown but ± d.t

1. Genetic: Exact genetic Connect= hasn't been determined (ass. **HLA B7 & 8**). HLA < B7, B8

2. Enviromental:



(ppF) · **Precipitating Factors**:
- Spontaneous. (2/3)
- Trauma
- stress
- inf.

· **Drugs**:
- Griseofulvin
- Dapsone
- INH
- Penicillamine

Forestabilished lesion → · **Exacerbating Factors**: Sunlight, Cold, Premenstrual.

C/P: Classical DLE lesion ch. By:

· **Discoid plaques**: نحدة إضاحية

(No)
- Single or Multiple
- Well defined
- Erythematous
- Show well formed adherent scales that Extend into a (Patulus) hair follicles « **Follicular plugging**
→ if this plug is removed → Chic Sign Called « Tin tack, Carpet tack or Cat tongue »

"Rook"
Tin Tack Sign ± seen in P. foliaceous

↓ • Healing of the lesion:

يحدث ويسيب ٤ حاجات
مميزة جداً

3- [• Atrophy
4- [• Scarring

"أولهم جرثاً"
1- [• Telangiectasia
2- [• Dyspigm = Hypopigm: in center / Hyperpigm: in periphery.

• Site of the lesion:

1- Skin: usually sunexposed ??
2- MM:
   - oral: LP or DLE picture or Leukoplakia
   - Genital: vagina, anus
   - ocular: → Ectropion.
3- Hair: → Cicatricial Alopecia.
4- Nail: →
   - subungual Hyperkeratosis.
   - red blue plate.
   - Longit. striae.

(4)

Clinical Varieties of DLE (13)

1- Localized: to head & Neck (أكثر Cheeks, Nose, Ears, Scalp)

2- Generalized (disseminated):
   1- More persistant.
   2- Resistant to Rx
   3- More prone to develop SLE (20%)

   4. similar to SCLE but with SCARS.

3- Hyperthrophic (Verrucous): simulating: LP, Wart or Nodular prurigo

4- Atrophic: Marked Atrophic Center simulating (LSA) (or) (Morphea)

5- Annular (LE Gyratus repens): migratory gyrate annular Erythemas.
   SCLE تشبه

6- Telangiectatic: Reticulated or Blotchy Telangiectasia (LE Telangiectoides) ↓ punctate atrophic scar.

7- Rosacea like: Similar to Rosacea but (No) pustules.
   - reddish dots
   - diffuse Erythema
   - flushing

8. Chilblain LE (Hutchinson)
9. Tumid LE. → dermal
10. LE panniculitis. (L. profundus) → S.C
11. LE profundus Hypertrophicus
12. LE/LP overlap synd.
13. Rowell's synd.

(2 synds)

14. Erosive palmoplantar (&) ↔ 16. Bullous DLE. (Exaggerated ↑ vaccular interface dem = Max Josset space (VIO) → Dermoepi Separat ↓ Bullae)
15. child hood DLE.

- **Chilblain LE: (Hutchinson's)**
  - **def** Chilblain like lesions (Circulatory disturbance) may appear some years after DLE in ≃ (6%) of cases. (but ± occur (rout) it)
  - **sex**: F > M
  - **clp**: • usually ♀, smoker, living in cold areas
    - **lesion**: Chilblain like (red or dusky purpule papules, nodules & plaques) at Cold Exposed areas (Fingers, Toes, Nose, Ear) الأطراف
    - (≃15%) of cases will → SLE.
  - **path** → as DLE
  - **Lab** → usually +ve Anti Ro & (anti Cardiolipin) وطرق
  - **tt** → DLE may remit but Chilblain LE persist. Rx ttt

DLE غالب بيحصل بعد سنوات ولكن ممكن يسبقه أو يحدثوا معا

إزاى تفرقه عن Chilblain العادى؟؟
⊙ Telangiectasia at Nail folds

- **Tumid L.E (LE Tumidus):**
  - **def.** dermal form of LE (No epidermal affect).
  - **clp.** plaques on photosensitive areas:

Urticarial like lesions in LE patients may be:

1. Urticarial Vasculitis
2. Tumid LE

- Erythematous
- Swollen
- brawny
- Tense
- ± annular
- Clear during winter & ✓ (doesn't) leave pigm. or scars.

→ "urticaria like" (but > 24 hrs)

- Pathology
  1. No epidermal changes (Not as DLE) XX as < Follicular plugging & VID
  2. Marked Patchy Lymphocytic dermal infilt. < Interstitial (superf. & deep) perivascular periappend. (Dense)
  3. Mucin deposition.

NB
- بعض يعتبرها نوع من DLE والبعض يرفض
- لسه موجود VID في DLE

HL ← Another syn.: papular & nodular Mucinosis of Gold or "Lupus Mucinosis."

(Lp) • Lupus Panniculitis (L. profundus):

- def: LE affecting mainly S.C.T with little or (No) dermal or DEJ affection
- sex: M:F = 1:4
- Clp: it may occur in ass. (e) DLE (60%) or SLE (or) as an isolated finding
- lesion: Multiple, firm, Movable S.C Nodules (usually) affecting: Face, deltoid area, Trunk, buttocks & Thighs. The overlying skin usually NL but may show Atrophy, DL or poikiloderma. Healing → Cup shapped depressed scar (Lipoatrophy) may ulcerate.

site:
- Face
- deltoid
- Buttocks & Thighs.

Skin: Normal, Atrophy, DLE, Poikil...

Path. « only S.C.T affection with Little or (No) dermal or DEJ affect^): Salient Histologic Features:

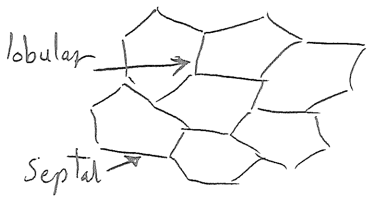
↓ (mostly lobular ± — Mucin / Vasculitis) الملخص

[1.] **Mostly Lobular panniculitis**: ē Lympho-histiocytic infiltrate & ± plasma cells & ± Germinal Center format^

May represent Lymphoprolif. dis. related to CTD ā has → Indolent Biologic Behaviour.

[2] **Vascular changes** (vasculitis): ± Lymphocytic Vasculitis

- prominent Endoth
- Thrombosis
- perivascular fibrosis (onion skin appearance)
- Calcificat^
- Fibrin deposit^ & fat necrosis → Hyalinizat^ of adipose lobules.



[3.] **Mucin deposition.**

NB: ع ناس اختلفوا ع التسمية : لكان ب LP (panniculitis) الجلد اللي فوقه
طبيعي هنا نفضل اسمه LP ولكن لو الجلد اللي فوقه
عليه DLE lesions يتغير اسمه ← L. profundus

NB: (30%) show classic DLE lesions.

[JB]

- **L. profundus Hypertrophicus**: L. panniculitis with Blackish "warty" skin overlying it.
- **LE/LP overlap synd** (LP: L. planus): clinically & Histologically bet(c) LE & LP but (IF) —suggest→ LP.

(H/P) ٣ أنواع

- There are 3 related Conditions:

DLE	Tumid LE	L Profundus
② • Epidermal & dermal Pathology • ± Mucin	③ • Dermal Path. • +ve Mucin • patchy infilt	③ • SC Pathology • ±ve Mucin • Vascular Changes

Rowell's Synd (EM Like lesions + CLE)

- Criteria for Dx : (Zeitouni 2000, BJD)

A. Major

1. presence of CLE (DLE, SCLE, SLE)
2. EM like lesions (with or without ± (MM) effect)
3. Speckled pattern of ANA

Target lesion ◎ لوحة النشاء EM

- Annular Erythematous Lesions ē Vesicular Bullae at Borders
  - ACrofacial.
  - Exacerbat- by Sunlight

B. Minor :

1. Chilblains.
2. Anti Ro or La
3. +Ve RF.

- For Diagnosis, 3 Major + 1 minor.

Dx Patient ē L.E who develop EM How to diff??

- No ppt factors e.g HSV inf.
- Clinic Serology of Rowell's ← ANA, Anti Ro - La, RF
- ↑↑ Cs & antimalarial.

- Rowells synd if very severe (may) progress to TEN-like. (JAA 2003).

- Pathology
  - KC Necrosis
  - Focal perivascular lymphocytic infiltr. Near the Basal layer
  - dermal Edema

- childhood DLE الوبية M:F = 1:1, FH: +Ve 25%, 50% → SLE

Family History → (25%)

SLE → (50%)

Diagnosis of DLE: (3)

[A]. Lab: (Serology) مهمة

- 30% → +ve ANA (Homogenous > Speckled) "low titer"
- < 5% → +ve Anti ds DNA, anti Smith, anti Ro [لو ايجابي يبقى معناه انه هيتحول الى SLE.]

↑ Serum Ig، ابقى اكتبها

- [• Chilblain serology (Anti Ro & anti Cardiolipin)
- • Rowell's serology. (ANA, Anti Ro, La, RF)
- +ve RF.
- false +ve serology for Ø.

(Others) → ↑ESR, Anemia, ↓C, leukopenia

[B] DIF → Lupus band test (LBT) < +ve in lesional (90% in sun exp., 20% in sun protected); -ve in Non lesional.

→ C5b9 test: 60% (+ve) in lesional skin only (at DEJ)

[C] Histopathology:

[A] Epidermal:
(3) <
- Hyperkeratosis ē Follicular plugging
- Atrophy of St. Malpighii.
- VID ē BMZ thickening (مهم), Colloid bodies, pigmentat.

[B]. Dermal:
(3) <
- Collagen degenerat.
- Patchy lymph. infiltr.
- ✓ Mucin deposit.

مهم | NB

① Relation to SCLE & SLE:

- DLE occur in ~20% of pt < 15-20% of SCLE Cases; 20-30% of SLE "
- Progression to SLE: < 5% of Adult Cases; 50% of children Cases.

أخطر الأنواع: ① disseminated DLE ② chilblain LE ③ childhood

Predict. of pr. to SLE

Types:
- Arthr.
- Anemi.
- leukop.
- ↑ESR
- ↑ANA

- Malignant changes (SCC) may develop specially on top of "hypertrophic lesions".

② Does DLE ass. ē systemic Manifs?? "yes" < Arthralgia; Raynauds

Treatment of DLE

(D.Darwati)
داروتي

Topical

A. General Measures (All cases)

1. sunprotection program → behavioral alterat° / sunprotective clothes / sunscreens > 15 SPF
2. Avoid ppt- & Exacerbating Factors. also (Smoking)
3. Vit D3

B. Topical Medications:

1- Topical Cs (potent or super potent ē or without ± occlusion)

دايرى
غالباً
فى مناطق
scalp

2- Intralesional Cs: 5-10 mg/ml every 4-6 wks.

3. others:
- Calcinurin inhibitors (CIs) (facial lesion)
- Retinoids (Hypertrophic DLE)
- Imiquimod (Anecdotal)
- Cryo.
- IFN-α (IL)

Systemic

ⓐ indicat°:
1. Failed Topical ttt
2. Progressive DLE (to SLE)
3. Disseminated ~.

↓ أهم

Antimalarials

Others
- Cs ✓
- Azathioprine
- MTX
- Cyclosporine
- Thalidomide ← مهم
- Retinoids ✓ ← "if Hyper Keratotic"
- Dapsone
- Clofazimine
- Vit. E (600/d) ← فيتامينات
- B-Carotene (150/d)
- Danazol
- auranofin

• Other Recent lines ادا طروحت

٣
- Cefuroxime (500 mg/d for 1.5 ms) ← لمدة
- phenytoin.
- Excision.

الروشتة

• Best ttt (of choice)

Sunprotect° + Topicals Cs + Antimalarial

SCLE

سؤال امتحان Q

- **Epidemiology:**
  - **Incidence:** (10%) of CLE cases
    - ↑ incid. of HLA ← DR3 (دی), DQ1, B8
    - ≥ 50% of cases show ≥ 4 ACR criteria for SLE diagnoses. (mild SLE).
    - [10-15%] will → severe (SLE)
  - **Age:** [15-70 ys] (average 43 y.)
  - **Sex:** M: F = [1 : 3] (4)

Clinical picture

1. photosensitivity
2. Cut. Erupt.
3. Mild systemic affect.

SCLE lesions

(A) Classical SCLE: sudden onset of: Asymptomatic Non scarring photosensitive Erupt.: ±

1. Papulosquamous (psoriasiform) (2/3)
2. Annular (Polycyclic) (1/3)

(B) SCLE subtypes

1. Drug induced SCLE
2. Neonatal LE (NLE)
3. Complement deficiency Synd. (C2d)
4. Others: Oriental & Late onset, Rowell's

Mild systemic

≥ 50% show ≥ 4 ACR Criteria of D of SLE But mild form

usually arthritis

others
- Alopecia
- leukopenia
- DLE (20%)
- SS.

Clinical Picture & Varieties

Photosensitive Erupt. ch. by

Erythematus scaly papules which evolve into either: annular (polycyclic) or Papulosquamous (Psoriasiform)

usually asympt. & has striking onset after sun exposure

[B] may Resolve with
- Telangiectasia
- Dyspigmentation (sp. Hypo or depigm)

But NB Atrophy or Scars (Central Hypo & periph Hyp)

. Sites → sunexposed Areas: [Photosensitive Area]:
- Face (mid facial skin spared but affect the sides)
- Neck
- V-shapped Area of chest.
- Shawl area (outer upper arms) & upper back

[Diagnosis]
1- Serology
2- DIF
3- Histopathology.

[Serology & DIF] "احفظ لو سمحت"

. [4 +ve]
- Anti Ro (SSA) (80%)
- Anti La (SSB) (30%)
- ANAs (80%) [Homogenous]
- Lupus band test +ve in:
  - 60% of Lesional skin
  - 30% of NL skin. (non Lesional)

[Pathology] as (DLE) but:-
- ↑ Marked: Epid. atrophy
- ↓ less Marked:
  - Hyperkeratosis
  - Follicular plugging
  - VID & BM thickening

[Drug induced SCLE]

@ Drugs:
- Thiazides (Commonest)
- Terbinafine
- Griseofulvin
- Aldactone
- Naproxene
- Diltiazem = [Naloxone, Diltiazem]
- Antihistamines

Q

Neonatal LE (NLE)

(EM 2009)

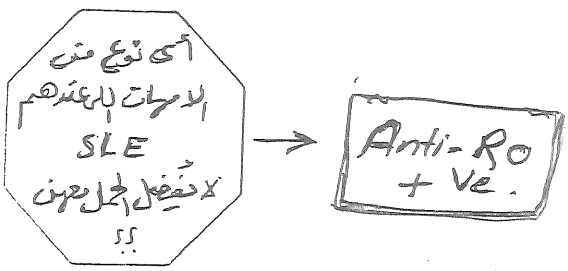
- def. Rare disorder caused by Transplacental passage of Maternal Antibodies & Ch BY: Cardiac, Cutaneous, Hepatic & Hematologic manifs. (2C, 2H)

- Risk Factors:-
  1. Mothers ē HLA B8 or DR3 (SCLE ē)
  2. Mothers ē: +Ve (Anti-Ro, Anti-La & U1RNP)
  3. past History of NLE (↑ incid From 1% → 25!)

- NB: the Mother
  - at time of delivery They are usually NL but can develop either defined or undifferentiated
  - → Autoimmune disorder as:
    - SLE or SCLE
    - SS (Sjogren Synd)
    - undifferentiated Autoimmune Synd (AUS)
    - Rheumatoid arthritis. (R.A)

Pathophysiology — see below.

- Epidemiology
  - Age: bet. birth – 1st few mns of life.
  - Sex: (F) slightly > M



Pathophysiology (HL)

The mother produces immunoglobulin G (IgG) autoantibodies against Ro (SSA), La (SSB), and/or U1-ribonucleoprotein (U1-RNP), and they are passively transported across the placenta. The presence of maternal anti-SSA/Ro and anti-SSB/La antibodies increases the risk of bearing infants with neonatal lupus erythematosus. These autoantibodies can be found alone or in combination; however, anti-Ro is present in almost (95%) of patients. Mothers of patients with neonatal lupus erythematosus may have defined or undifferentiated autoimmune disorders, such as systemic lupus erythematosus, Sjögren syndrome (SS), undifferentiated autoimmune syndrome (UAS), or rheumatoid arthritis (RA).

mother → develop (4)

The 52-kd SSA/Ro (Ro52) ribonucleoprotein is an antigenic target strongly linked with the autoimmune response in mothers whose children have neonatal lupus erythematosus and cardiac conduction disturbances, mainly congenital heart block. Anti-SSA/Ro52 autoantibodies recognize the Ro52 protein cardiac 5-HT4 serotoninergic receptor and inhibit serotonin activated L-type calcium currents (ICa). This effect could explain the pathogenesis of the cardiac rhythm disturbances, which lead to an increased risk of diminished cardiac output and the subsequent development of congestive heart failure.[2] However, these conduction defects are caused not only by Ro antibodies but also by anti-SSB/La antibodies and other autoantibodies against cardiac adrenoceptors and muscarinic acetylcholine receptors.

Endo... fibroblas...

The skin manifestations of neonatal lupus erythematosus occur in the first month or later in life and are mainly due to the presence of anti-SSB/La antibodies, but they may be mediated by other antibodies. Most infants have cardiac and dermatologic manifestations, but some of them may also have hematologic and liver involvement

dp (4) *

CIP

1. Cardiac (6%): Cong. HB → DD; Need pacemaker → 20-30% Mortality rate. (also myopathy)
2. Cutaneous (50%): as SCLE but resolve spont± leaving (6-12 ms) atrophy, Telangiect. & dyspigm. (but) no scar. (غالباً عند البنات)
3. Hepatic: Hepatobiliary dis.
4. Hematologic (26%): Sp. Thrombocytopenia ±Neutropenia & Anemia
5. Skeletal:
   - Hydrocephalus
   - Macrocephaly
   - Dysplesia

Note.

Lesions Clically Periorbital

(owl Eye)

Raccoon sign

(ترتيب الإصابة Periorbital → Scalp → arms → legs & Trunk)

"NB ± Small angioma Like" papulonodules.

diseases & Raccoon Sign?!

100% +ve Anti Ro

also: [anti La/SSB, anti U1 RNP

♀ ✓

Acute Cutaneous L.E (ACLE)

- This Type of Cut. L.E usually ass. with Systemic Involvement So it will be discussed as (SLE).
- def. → يعرف
- Pathophysiology: → يعرف
- Epidemiology: • Age: • in ♀: 14 - 64 Ys (Period of Sex Hormone product)
  - in ♂: ↓ No predilection. ← Age.
- Sex: M : F = 1 : 9

- This may Explain The role of Sex Hs.
- SLE More Common in Klinefelters.

- CIP: (A.) CIP
  (B.) Criteria For ⊠ (ACR)

"يعرف" + روماتولوجي **A CIP**

2 C
1. General Manifestations
2. Musculoskeletal
2 C
3. Cutaneous
4. CNS
2 C
5. Heart = Cardiac
6. Chest
7. Kidney
8. GIT
9. Ocular
10. Hematological

Commonest Manifestations of SLE??
1- General
2- Musculoskeletal
3- Cut
4- Kidney
← a/s the First manifs.

NB:

- 90% < Fever, arthralgia
- 80% : skin (يعني)
- 70% : Renal
- 50% : L.N
- 40% : Pleurisy & Rayn.
- 30% < CNS, Heart

[1] General Manifs: (90%)

- Fever (90% ± d.t < Inf. / Flare of dis / Drugs).
- Fatigue
- L.N
- W.t < loss: d.t Exhastion from the dis. / gain: d.t Cs ### or N.S

[2] Musculoskeletal: (90%)

Myopathy ē mild Myositis & ↑ serum Aldolase (Not Alk. phosphatase)

1. Arthritis & Arthralgia: mainly small joints & ± migratory ASYmm. (DD. RA)
2. deformity:
   - Rhoid like ē S.C. nodule
   - Jacoud Arthropathy.
3. Avascular Necrosis of Femur Head: (d.t < dis. / Cs)

[3] Cut. Manifestations of SLE: (80%) (Acute cut L.E)

* Specific (show chic Histopath. of LE = VID)

آ د ل ٣ ما ها ع

ACR Criteria

[1] Malar Rash
[2] Photosensitivity
[3] DLE lesions
[4] Generalized Morbilliform (Maculopapular) rash on:
- Extensors: limbs, hands (spare! Knuckles)
- Photosensitive areas.

[5] TEN-like SLE. (ASAP) [Acute Synd of apoptotic Pan-Epidermolysis]

الترتيب مهم

* Non Specific

1 - Vasculitis
2 - Vasculopathy
3 - Hair
4 - Hands
5 - Legs
6 - Others

> Cut. manifs present in 80% of SLE cases
> " " are the 1st to appear in 25% of SLE cases. Malar Rash

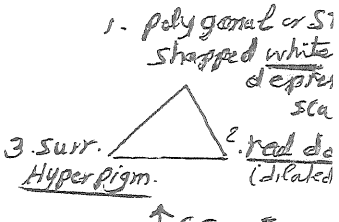
• Non specific Cut. Manifs:-

① Vasculitis:

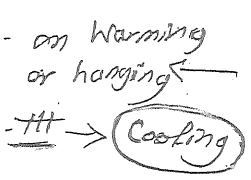
- LCV (painful, palpable purpura)
- UV. (urticarial Vasculitis)
- PAN like lesions. (Polyarteritis Nodosa).

② Vasculopathy (ou) :

- ulcerations
- Livedo Reticularis
- Acrocyanosis
- Degos like lesions
- Atrophie blanche like lesions.



- Erythromelalgia (Erythramalgia)



③ Hair: Loss in SLE. "cicatricial"

"d.t slow anagen" → cicatricial
- Lupus Hair (Coarse, dry, fragile frontal Hair → unruly appearance with shortening & Breaking off)
- T.E
- AA. [patchy]
- CIC. Alopecia (d.t DLE lesion).

④ Hands:

- periungual Erythema & Telangiect. (Nail fold) → CTD
- Palmar Erythema
- Raynaud's phenomenon.
- sclerodactly.

"e ragged cuticle."

⑤ Legs:

- Ulcers
- Thrombophlebitis.
- Vasculitis
- Vasculopathy

⑥ Others.

- L.P
- AN (Acanthosis Negricans).
- Mucinosis
- symm. Papular eruption of Extrem.

4. CNS:

- Seizures.
- Psychosis.
- Migrain.
- Hemiparesis.

5. Heart:

- Pancarditis
  - Pericarditis: Commonest Cardiac Manif.
  - Myocarditis: Cardiomegally & gallop.
  - Endocarditis: Verrucous
    - Libman Sacks type (non infectious E
    - affect Mitral & Tricuspid (MT)

6 Chest:

- Pleuritis,
- Parenchymal lung dis (More in elderly).

7. Kidney: « Lupus Nephritis »

- Classification Acc. to (ISN): → int. Society of Nephrology
  - Class I: minimal Mesangial
  - Class II: Mesangial Prolif.
  - Class III: Focal "
  - Class IV: diffuse "
  - Class V: Membranous
  - Class VI: sclerosing.
- Histopath: chic **Wire loop** d.t Subendothelial deposits of Fibrinoid Material.

8 GIT:

- NVD
- splenomegaly
- Lupus Hepatitis ✗
- ulcerative colitis.

9 Ocular

- KCs (Kerato Conj. Sicca)
- Corneal Hge & dysplasia
- Retinal Hge.

10 Hematology → See ACR

(B) Criteria For Dx of SLE.

THE AMERICAN COLLEGE OF RHEUMATOLOGY 1982 REVISED CRITERIA FOR CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds → & nasal bridge.
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis (2)	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion → ≥2
6. Serositis	a) Pleuritis–convincing history of pleuritic pain, rubbing heard by a physician, or evidence of pleural effusion *OR* b) Pericarditis–documented by ECG, rub or evidence of pericardial effusion
7. Renal disorder (urine Analysis: protein, Casts)	a) Persistent proteinuria greater than 0.5 g/day or greater than 3+ if quantitation not performed *OR* b) Cellular casts–may be red cell, hemoglobin, granular, tubular or mixed
8. Neurologic disorder	a) Seizures–in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis or electrolyte imbalance *OR* b) Psychosis–in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis or electrolyte imbalance
9. Hematologic disorder (4) (CBC)	a) Hemolytic anemia with reticulocytosis *OR* b) Leukopenia–<4000/mm3 (on two or more occasions). OR c) Lymphopenia–<1500/mm3 (on ≥2occasions) OR d) Thrombocytopenia–< 100 000/mm3 (in the absence of offending drugs).
10. Immunologic disorder (Serology)	a) Anti-ds DNA. *OR* b) Anti-Sm *OR* c) +VE antiphospholipid antibodies *based on:* (1) +ve anticardiolipin (2) +ve anticoagulant; or (3) false- positive serologic test for syphilis (positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test (FTA-ABS)) [i.e Typical beaded pattern].
11. Antinuclear antibody (ANA)	An abnormal titer of antinuclear antibody by immunofluorescence (or an equivalent assay) at any point in time and in the absence of drugs known to be associated with 'drug-induced lupus' syndrome → >1:160

NB: ± unilat, Cause di, ± Asymp

→ Commonest: Post. surface of hard pala

- For diagnosis: ≥ 4 Criteria
- ACR has: Sensitivity : 85%, Specificity : 95%

Some NB on SLE.

1. What is the significance of

- Raynauds → ↓ incid. of Renal affect
- UV → ↑↑ " ~ " ~
- Livedo reticularis → CNS affect
- Cut. + CNS affect → Antiphospholipid Antibodies.

UV → Pain Pull
>24 h
Pigm
H/p of vasculitis
ass ē Nephritis

2 Pregnancy & SLE: (Rook)

A Effect of Pregnancy on SLE:

- 1st trimester → Exacerbation (↑↑) (after delivery: ↑)
- Next 6ms → improve (↓↓)

- if SLE is in remission 6ms before delivery → Pregnancy will pass uncomplicated.

B Effect of SLE on Pregnancy:

dead:
1- Abortion
2- IUFD

live:
3- NLE
4- Live birth (Normal Neonate): (Specially if There is remission on the last 6ms)

NB

(i). **Risk of fetal loss is ↑↑ if:** (AP Synd.)

- Abortion
- IUFD

1. History of previous loss.
2. " " Thrombosis.
3. +Ve Anti Cardiolipin & Anticoagulant antibodies.

So if:

+Ve Anti Cardiolipin & Anti Coagulant +

- History of previous loss or Thrombosis → • Aspirin + • Cs.
- -Ve History → No need for ##.

Cs in early preg. & in Large doses → cleft palate

(ii). **Risk of NLE** if: → +Ve Anti-Ro.

C OCPs:

- Estrogen containing should be avoided. Safe Methods are IUCD, Mechanical Methods or Progest. only pills.
- (Est. → SLE exacerbation).

D Breast feeding:

allowed if the mother on Cs or Aspirin

Not other Immuno-Supp. XX

3. Types of SLE : (HL) (X)

1- Classical Type
2- Childhood SLE:
   - bef. 3-5 Ys
   - M:F = 1:4
   - More Severe renal & CNS affect
3- Familial:
   - rare
   - usually ass. with Hypergammaglobulinemia
   - Concordance in Monozygotic Twins (70%)
   - several other Family members have intermittent symptoms as (Synovitis & +ve ANA)
4- SLE of Elderly:
   - > 60 Ys
   - less incid. of renal & GIT
   - ± ass. ē Ss & Lung affect
   - +ve Anti Ro & La / HLA D3.
5- ANA -Ve SLE:
   - Causes: 1- using non Human substrate
     2- if all ANA directed against ssDNA
     3- SCLE ē photosensitivity (ANA -ve Anti Ro +ve)
   - C/P:
     - Malar rash
     - Photosensitivity
     - oral ulceration
     - Papulosq. or Annular lesions of SCLE
   - Invs: +Ve Anti Ro, anti La & anti ssDNA
     By Time → with ANA +ve.
   - Hx: Cs (topical) & Antimalarial.

6- SLE ē genetic C2 deficiency

- AR ch BY SLE + ↓C2 & C4.
- C/P . Cut . marked photosensitivity, marked & severe lesions ē Atrophy . Telangiectasia . Scarring .
  - CNS & renal affect

7- others: [Rowell's synd. / Oriental SLE.

Q ✓

8- Drug Induced LE ---- → see end

(Includes)

Drug induced SCLE

(زي اللي فات)

- SCLE like c/p ē +ve AntiRO/SSA
- Commonest drug: Hydrochlorothiazides, ACEI
- + [Terbinafin, Griseovalfin (others see SCLE)
- + [Naloxone, Diltiazim

Drug induced SCLE → Anti-Ro (DNA)

خط جيدا.

Drug induced SLE → AntiHistone

Drug induced SLE

4 important Drugs: (5)

HIP - DPM → Minocycl

- H: Hydralazine
- I: INH
- P: pro-Cainamide
- D-penicillamin

HIP → SLE like picture but ē (rare) Cut. ↓↓ & renal affection.

- serology [+ve Anti Histone. / +ve ANA.
  - (-ve Anti dsDNA).
- resolve ē stop of the drug.

DP → - SLE like c/p . ē frequent Cut. & ↑↑ renal affection.

- Frequent (+ve Antids DNA).

• NB: INH ass ē 5-10% risk of renal.

• Investigations For L.E

- Lab.
- Rad. { Joint XR, CXR, CT, MRI, Echo.

Rapid Screening tests (3) possible

- CBC
- ESR & CRP
- Urine analysis.

NL ê absence of (inf)

- CRP: React more acutely
- ESR: Lags behind dis. changes

Both → not indicative of dis. Activity

(3)

- Serum Complement
  - ↓ C3 & C4 → Active SLE & LE Nephritis
  - ↓ C2 & C4 → Complement deficiency synd. (C2d).
- Serum Gammaglobulins ↑↑
- Serum anticoagulants (Lupus Anticoagulants). (30%)

(3)

- Coomb's Test (+ve).
- Rhoid factor (+ve).
- W-R: False (+ve) for > 6ms. (EFR)

NO Established Criteria For assesment of Progression.

(2) Tests.

- L.E cell Test.
- Lupus Band Test

- Autoantibodies: L.E is an autoimmune disease That is Ch. By Formation of auto anti-bodies against Soluble Nuclear & Cytoplasmic antigens ẅ include:-

  - ANA
  - Anti ds DNA
  - Anti Ss DNA
  - Anti Sm antibodies.
  - Anti-n RNP.
  - Anti RO (Ss.A) → NLE, Drug Induced SCLE
  - Anti La (SS.B).
  - Anti phospholipid antibodies.
  - Anti Ribosomal.
  - Anti histone → drug induced SLE

• L.E Cell Test: (AIHA مش بيستعمل لوحده)

. This Test depends on the presence of L.E !? Factor (autoantibody against Nucleoprotein)

. Patients serum (موجود فيه) + NL WBCs → The L.E factor diffuses into the WBC's Nucleus:

↓ destruction

Nuclear damage & disintegration of Nuclear material

- phagocytosed by another WBCs (that escape the damage).
  - ↓ Wright's stain.
  - • Neutrophils ē:
    - Large
    - Rounded
    - Homogenous
    - Basophilic

  Bodies

  Called: L.E Cells

- Surrounded by another WBCs.
  - Called: L.E Rosette.

. This test ch BY:

↳ Specific Not sensitive.

- +Ve in 8% SLE
- +Ve in 2% DLE

N.B: Not sensitive; +Ve in DLE, SSc, RH.A

What is
- L.E Cell factor
- LE Cells
- LE Rosette

؟؟ (هتقوى)

Lupus Band Test

It is DIF test to detect IgG, IgM & C3, IgA (Linear or granular) at the Sublamina densa of BMZ (SLD / BMZ)

← Done By taking Biopsy from both Lesional & Normal skin → Then do DIF test..

	lesional skin	non lesional sunexposed skin	non lesional sunprotected skin
DLE	90% +ve	-ve	-ve
SLE	90% +ve	90% (60-100%)	≈ 50% (32-91%) (suffer arm 70 / buttock 30)
SCLE	60%	30%	-ve

- Significance:

Differentiation & prognosis

- bet DLE & SLE

① Prognosis of DLE Cases that will progress to SLE (if become +ve in non lesional)

② Prognosis of SLE severity: if it is +ve in sunprotected uninvolved skin of SLE cases → Correlates well ⓔ dis. activity, → Hence ⓟ severity of Renal affection.

- +ve Healthy → sunexposed → SLE
  → sunprotected → SLE + Renal

Autoantibodies

• ANA Test (AN Factor).

- ⊙ Very sensitive: (+ve in >99% of SLE Cases).
- ⊙ NOT specific: because it is +ve in: [but lower titer]
  - NL individuals (5%)
  - Old age
  - Pregnancy
  - Mg
  - Drugs (Minocycline).

+ve ريكس
- SLE: 90%
- SSc: 40-80%

- titer > 1:160 (titre) or (160-320) → Diagnostic
- What is ANA -ve Cases ?? ← Non human substrate against ss DNA.
  SCLE & photosensitivity.

Significance - So this test used as: Screening test
to help rule in or rule out SLE Cases.

- Methodology:

Patient's serum (Containing ANA)
+
Substrate: Human Tm Cell line (as Hep-2 cells) ← derived from Human Laryngeal Cell line.
(Cultures of Eos. sec)

← "Mouse liver ortid. Sections"

↓ Incubation

Add Fluroscent Labelled anti Human γ globulins

↓

Comment on (2) things:

- ANA titer
- Pattern of Fluorescence.

(3) Comment on:-
- Substrate
- titer
- pattern.

ANA test (FANA)

Titer

① Higher titer > 1/160 is diagnostic & the higher The Titer the more the significance of the dis.

Screening (so used to rule in (or) rule out SLE Cases).

- but no relat to dis activity. progress. duration.

② Higher titer:

ⓐ present in: SLE. MCTDs. SSc.

ⓑ against ??? DM & PAN

ⓒ Higher Titer in NL individual means Will progress to SLE.

Pattern of Fluroscence

(See the table)

- Peripheral stain is diagnostic
- other patterns (less Common).
  - Homogenous
  - speckled
  - Nucleolar

ANA pattern	Antigen	Diagnosis	prognosis
Peripheral (Membranous)	ⓝ DNA (dsDNA)	→ SLE (SSc-Mg)	Poor
Homogenous	Ⓗistones nDNA	drug induced SLE → SLE	Good Poor
Nucleolar	Nuclear RNA	SSc, SLE	Poor
Centromere	Kinetochore	CREST	Good.
Speckled	Ⓢm nRNP	→ SLE MCTD	Poor Good

- **Anti ds DNA** (Anti native-DNA ; Anti n-DNA)

Keep it ↙

Specific
Not
sensitive (60%)

Asse

- Can be measured by (RIA, ELIZA, IOIF utilizing Crithedia Luciae as a substrate).
- Specific but not sensitive (+ve in (60%) of SLE cases).
- Ass. ē: severe renal affection → Poor Prognosis

peripheral pattern of ANA

- **Anti ss DNA** → not specific: (+ve) in
  - SLE: 60%
  - DLE.
  - MCTD.

Keep it

- **Anti Sm antibodies**:

Very specific
Not
Sensitive

- The (most specific) test for SLE
- Non sensitive (+ve in (20%) of SLE cases)
- Ass. ē ↑↑ incid. of renal & cut. affection →
- More relevant when Anti ds DNA is -ve.

Poor Prognosis

- **Anti nuclear Ribonucleo Protein** (nRNP Abs): [U1RNP]

Ch By

↓

Speckled pattern

- **MCTD** (100%)

↘ good prognosis

- NLE

Anti La (SS-B)

- +ve in 10% of SLE Cases.
- +ve in 80% of SS & SCLE
- Usually ass. ē Anti-Ro. (See Anti Ro)

Anti RNP are
- Anti Ro
- Anti La
- Anti U1 RNP.

Anti Ro (SS-A) (Usually ass. ē anti La).

- NLE → 100%
- SCLE → 80%

- SSc/LE overlap → 75%
- Oriental L.E → 60%
- SS → 40%
- SLE → 30%

Anti-Ro ≈ Anti-La.

Anti Histone

Drug induced L.E

NB: 80% of SLE
50% SSc ✓

"Homogenous" → Homogenous Pattern

good prognosis

Anti-Ribosomal Abs → Lupus Cerebritis.

Antiphospholipid Abs (Anti CL & LA Antibodies)

- Cardiolipin
- Coagulant

(See APS)

Histopathology of CLE

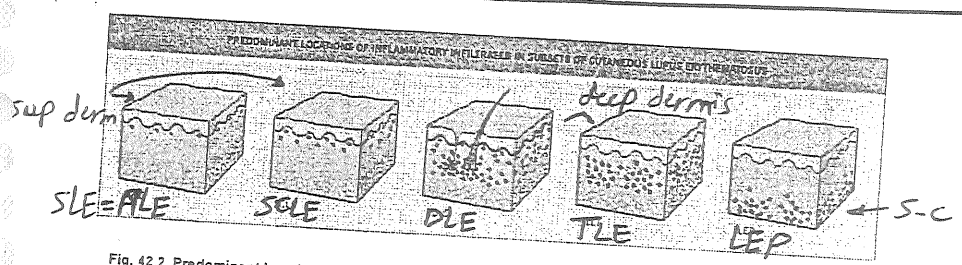


Fig. 42.2 Predominant locations of inflammatory infiltrates in subsets of cutaneous lupus erythematosus. The types of cutaneous lupus erythematosus are: acute cutaneous lupus erythematosus (ACLE) subacute cutaneous lupus erythematosus (SCLE) discoid lupus erythematosus (DLE) lupus erythematosus tumidus (LET) and lupus panniculitis (LEP); the latter three are forms of chronic cutaneous lupus erythematosus. The primary locations of the infiltrates are as follows: superficial dermis, ACLE and SCLE; superficial plus deep dermis and periadnexal, DLE; superficial and deep dermis, LET; and subcutaneous fat, LEP.

Histopathology of CLE

شرح تفصيلا → 1- DLE → Epid, lower & upper dermal (Deeper Pathology)

DLE تيبهان برزال للتخرجة النظر لكبون [→ 2- SCLE, → 3- SLE] → Epid. & upper dermal

△1 DLE Pathology:

(مهم جدا كيف نخمن)

(A). Epidermal changes: –

1. Hyperkeratosis with Follicular plugging
2. Thining (Atrophy) of St. Malpighii
3. VID: Vacuolar degeneration of Basal [BCL] Cell Layer ass. with

3 فوق

Dermis →
- BMZ Thickening مهمة
- Colloid bodies
- Pigment incontenance.

(B). Dermal changes: –

1. degenerative Collagen changes:

3 تحت

- Edema
- VD
- RBCs extravasat$^{\frown}$
- Collagen Hyalinization
- Fibrinoid Necrosis

3 – Mucin deposit

2. Lymphocytic infilt.: ↑ Patchy superficial & deep.

sites ③
- periappendageal
- perifollicular
- interstitial

[also ± lichenoid infilt.]

(NB) → Rook: For Diagnosis We should have at least 2 of 3: –

1. Vacular degen → VID
2. Degenerative collagen changes
3. Patchy Lymphocytic dermal infilt.

DD of LE

Clinically & HP] diseases ch By chr. Erythematous Indurated plaques & Patchy der. Infilt. by pathology — 5Ls dise

5Ls disease
- LE (Tumid)
- Light Erupt= (PML)
- Lymphocyt'c Infilt. of Jessner
- Lymphocytoma (Cutis)
- Lymphocytic Lymphoma

Tumid LE
- NL Epid
- Marked dermal infilt.
→ Marked Mucin deposits

Jessner
- NL Epid.
- (No) Mucin Hydropic degen.
- deep dermal & ± SC infilt. (↑B-cells)

pMLE
- upper papillary dermal Edema
- dermal infilt. & some Neutroph
- (NO) Mucin Hydropic degen.

بعض لعينهم مرض واحد

L.E
Jessner
Mucinoses نوع منه
بعض لعين

((5Ls)) إما / أو

Lymphocytic Lymphoma
&
Pseudolymphoma (Lymphocytoma Cutis).

Both: (No) epidermal changes.

All → No (NL Epid): + dermal infilt

X
- HyperK
- Atrophy
- plugging
- VID
- DIF

But — الفرق بينهم

But infilt.

Lymphoma
- Bottom Heavy
- Indian Filling (Clear Cell.)
- Appendageal infilt & destruction

Pseudo
- Top Heavy
- Follicle like aggregate
- Grenz Zone.
- No Appendageal infilt. [Germinal Follicles]

Jessner
- Prominent B cells
- CD62-L +ve
- HLA DR-Ve
- T Cells.

TLE
- Marked Mucin.

pMLE
- upper papillary dermal Edema
- ± Neutrophilic infilt.

(updated EMed. 2010)

Treatment of SLE

→ depends on the Severity

Cut. LE [illegible]
- Sun protect
- Topical Cs
- Antimalarial

• Mild dis e.g
- Fever
- Cut. manifs.
- Musculoskeletal manifs.
- Serositis.

(Mild)

↓

• Antimalarial (HCQ) or MTX ± Cs (low dose).

[illegible]
- Sun protect
- Topical ttt as in DLE.

• Moderate dis.
- Nephritis: mild–Mod.
- Thrombocytopenia: ($20-50 \times 10^3$)
- Major Serositis.

↓

• Induct therapy ē (MP) (1gm/d for 3ds) then → Maintenance therapy ē (Cs + AZa)

• Severe dis
- Severe Nephritis. (See Classifical)
- Severe Thrombocytopenia ($< 20{,}000$)
- Severe hemolytic anemia.
- Lung Hge.
- Cerebritis.
- Abd. Vasculitis.

↓

• Induct ttt: MP + CYC (IV) → 1gm/m²/ × 7 doses (CYCloph.)

- **Complete resp.** → maintain ē AZA + Cs
- **Partial resp.** → Cycloph. 1gm/m² /3ms.
- **No-Respons** → Add:
  - rituximab
  - IVIG
  - Calcinev (CIs)

• First line of ttt (CLE [illegible])

A . Antimalarial
C . Cs
D . Dapsone

(HL) **New Immunomod.** ([illegible])
- Leflunamide
- Nucleoside analogues e.g Cytarabine
- rituximab

Serology of SLE

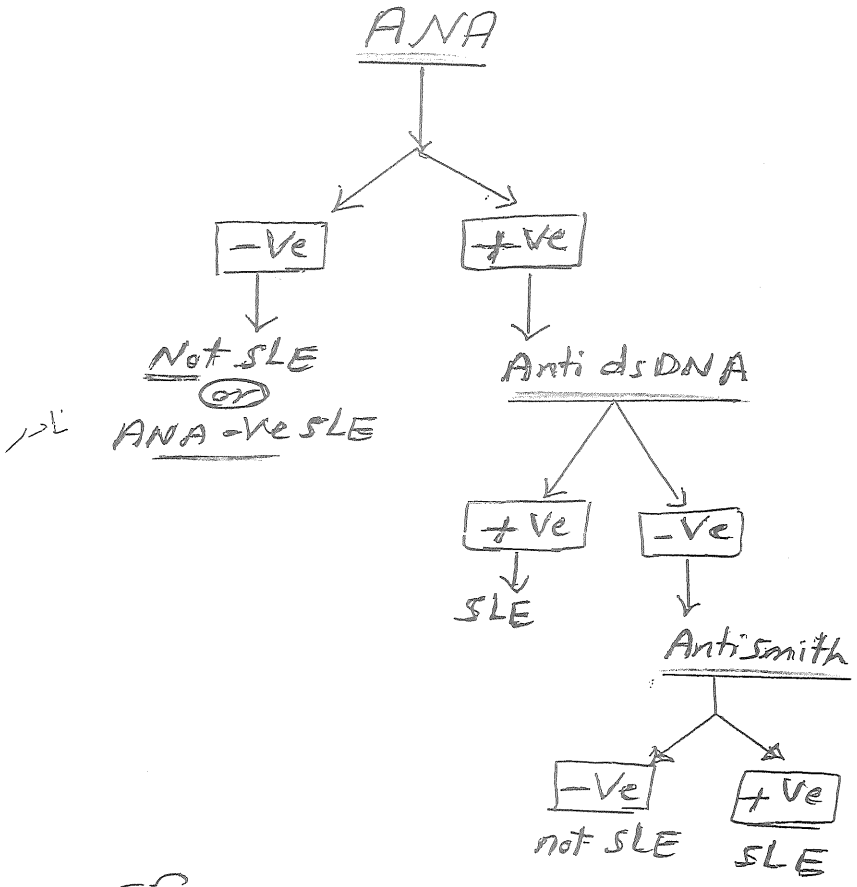
(9) Antibodies

- ANA → (90%)
- Anti ds DNA (60%)
- Anti Sm (20%)

- Anti-Ro (30%)
- Anti La (10%)
- Anti U1 RNP (nRNP)

- Anti histone
- Anti Ribosomal
- Antiphospholipid (30%)

Diagnosis of SLE ✓
(Approach For ⊘)



What is the significance of

- ANA: sensitive.
- Anti ds DNA (specific)
- Anti smith (Most N) → Severe renal.

- Anti Ro → NLE (low%), SCLE (80%) & ANA -ve SLE
- Anti-U1RNP → MCTDs (100%), NLE

drug induced

- Antihistone → DILE
- Anti Ribosomal (Lupus cerebritis; CNS affect
- Antiphospholipid → (33 pregnant)

SSc ← Antinucleolar / Anti Centromere → CREST

Dermatomyositis

Dermatomyositis (DM): chronic, idiopathic, immune mediated disorder that includes an inflammatory myopathy and characteristic skin manifestations (Muscle+skin affection);

Polymyositis (PM): is an inflammatory myopathy without the cutaneous findings (muscle affection without skin affection).

Etiology: unknown; may be due to: genetic, environmental agents (e.g., virus, drugs) and autoimmunity.

Epidemiology:

* M:F=1:2
* Age: 1.Adulthood type: average 40y 2.Juvenile: 5-14 y.
* Cause of death: Mg, infection, pulmonary and heart affection.

Clinical presentation of DM:

A. Clinical picture:

1. Cutaneous manifestations
2. Muscular manifestations
3. Systemic complications/associations

B. Clinical subtypes (see the table)

C.Criteria for diagnosis.

A. Clinical picture

1.Cutaneous manifestations:

A.Pathognomonic manifestations (2)

1.Gottron's papules: violaceous erythematous (Lichenoid) papules overlying the dorsal interphalangeal or metacarpophalangeal, elbow or knee joints.

2.Gottron's sign: symmetric, nonscaling, often atrophic violaceous erythematous macules or plaques, in the same distribution as Gottron's papules

= papule

= Macule or plaque

Gottron's papules = papules Gottron's sign: Macule or Atrophic plaque (لإتساع لون بنفسجي violaceous).

B. Characteristic manifestations (4)

1.Heliotrope erythema: violaceous purple erythema/edema at periorbital area (mainly) also cheek, temple and forehead.

2.Shawl sign/V-sign: Violaceous Erythema & scaling on shoulder and upper outer arms (Shawl sign) and V-shaped area of anterior neck and chest.

3.Periungual telangiectasias: *with ragged cuticle* (dystrophic cuticle).

4.Mechanic's hand: hyperkeratosis, scaling and fissring of hands due to *Gower's sign* (associated with an increased risk of interstitial lung disease and +Ve antisynthetase).

C.Compatible manifestations (2)

1.Poikiloderma atrophicans vasculare (poikilodermatomyositis): violaceous incontrast to that of LE which is erythematous. on Shawl/V shapped areas & buttocks

2.Calcinosis cutis: more common in children; firm, whitish/yellowish papules, plaques or nodules on the surface of the skin that may ulcerate and discharge chalky material. Most commonly present on the buttocks, elbows, knees or traumatized areas, *and is associated with increased disease activity and duration.*

D.Less common manifestations (6)

LP.

MG → death

Vasculitis

Panniculitis

- Holster sign violaceous Erythema at Lat thigh.

- Poikiloderma

Erythroderma

Facial swelling

- Scaly scalp (itchy)

Mg + hyperkeratosis

E. Rare manifestations:

3 OSIS (hyperkeratosis, hypertrichosis, mucinosis).

2 urticaria (urticaria and U.vasculitis).

Zebra-like stripes (centripetal flagellate erythema).

* Degos' disease.

2. Muscular manifestations

Common: Symmetrical proximal muscle weakness → difficult walking, getting up from chair, combing one's hair, dysphonia, dysphagia.

Less common: respiratory muscle weakness, visual changes, abdominal pain.

3. Systemic complications/associations

- Heart
- Lung
- GIT
- Kidney
- Organ Malignancy

* Heart: Cardiomyopathy.
* Lung: Aspiration pneumonia (secondary to respiratory muscle weakness), Diffuse interstitial pneumonitis/fibrosis (ILD)
* GIT: Large-bowel infarction (secondary to vasculopathy).
* Muscular: Muscle atrophy and calcification.
* Ocular: including iritis, nystagmus, cotton-wool spots, optic atrophy, conjunctival edema and pseudopolyposis.
* Internal malignancy.
* Renal: Nephritis.

ILD = interstitial lung disease

B. Clinical types. (See classification) (6 Types)

1. Adult DM
   - A. Idiopathic (classical) Type.
   - B. Paraneoplastic Type.
2. Juvenile DM (classical & Amyopathic)
3. Amyopathic DM (DM sine Myositis) & Hypomyopathic DM.
4. Adermatopathic DM.
5. overlap DM.
6. Drug induced ← Hydroxyurea, statins, DP.

1- Adult DM

A Classical (Idiopathic) DM. →

3 ← skin, Ms, syst

B- Paraneoplastic DM

(DM is one of paraneoplastic syndromes)

- Incid.: 10-25% of DM cases
  - Risk remain ↑ for 3-5 ys after Dx

- Risk Factors:
  1- Adult DM
  2- Women > 45 ys
  3- Amyopathic DM.

Amyopath
o+ > 45y
↓
Mg أدوية على

- Type of Cancer:
- Commonest:
  - Ovarian Cancer
  - Gastric "
  - Colon "
  - Lymphoma.
- less Common:
  - Breast Cancer → Seb Kerat
  - Cancer lung
  - ♂ Genital
  - MF.
  - MM (my Melanoma)
  - Kaposi.

So Any case of DM after age > 45 ys (Sp. Woman)

Follow up by
1- CA.125 (Cancer Ag) → Ovarian Cancer Marker
2- Mammography
3- TV US.
4- Gynecologic Exam.

كل ٣-٦ شهور على الأقل طول سنتين

+

also: CT < Chest. Abdomen. pelvis.

- others:-
  - PSA (♂)
  - occult Blood in stool
  - Colonoscopy (if appropriate Age, occult Blood in stool - symptoms) Fe def. anemia)
  - upper GIT Endoscopy (if -ve Colonoscopy, ...)

2. Juvenile type: differ from adult type in: (Juvenile 50%) (adult 15%)

* High incidence of calcinosis cutis, GIT complications, low grade fever, arthritis, cardiac conduction defects (RBB) and Gowers sign.

CC = Arthritis, Cardia, GIT, Gowers

↑ lung dse

* There does not appear to be any association between juvenile dermatomyositis and malignancy.

XX Mg

Arth 2C 2G

Mg

3. Amyopathic Type (Dermatomyositis Sine Myositis) (2-10%)

- def: patient with pathognomenic skin changes without clinical (or) Lab. evidence of Muscle involvement for at least 6 (2) years.
- incid. 2-10 % of DM Cases.
- CIP 1- Pathognomonic Cut. changes.

2- Commonly There are: arthralgia, Fatigue, pruritus, Lethargy & photosensitivity. → FLAPP

3- In some Cases: Clinical Myositis develops Later on & in other Cases There is already subclinical Myositis but can be detected by Non-standard Methods as (MRI).

4- ↑ incid of (Mg).

↑ Risk For (Mg).

Cut. Signs ± either

- No Myositis in 1st 6 ms → later on clinical Myositis.
- Subcl. Clinical Myositis MRI

4. Overlap DM (40%)

- The Patient has Criteria for (+) of DM & other AICTDs as SLE, (SSc), SS
- More responsive to (Cs) > Idiopathic DM.

- NB: Hypomyopathic DM :- skin rash (+) lab (or) Rad. Myositis without clinical Myositis.
  - may or may not → Clinical Myositis.

Skin Rash (+) lab / Radio → Myositis (−) clinical Myositis

5. Adermatopathic: Polymyositis with little or (No) skin affect

others:
- Hypomyopathic DM
- Inclusion Body Myositis

Criteria for diagnosis of DM/PM

A. Bohan Criteria (1977):

5 Criteria for DM:

1. Typical skin Rash
2. clinical — proximal symm. ms weakness
3. lab — ↑ ms Enzymes:
   - CPK
   - Aldolase
   - LDH
   - SGOT & SGPT
4. +ve EMG
5. +ve ms Biopsy

Diagnosis:

- definite D = skin manifs + 3 other criteria
- probable D = " " + 2 " "
- possible D = " " + 1 " "

Invs of DM

1. Ms < Enzymes / Rad: EMG, U/S, MRI / Biopsy
2. Skin: Biopsy → Non-specific.
3. Serology: Auto Abs.

Auto antibodies

[Serology is not sensitive so not useful in D.]

Highly specific

- 155 KDa &/or Se (80%) (Anti TIF 1γ)
- Jo-1 (20%) (anti synthetase).
- Mi-2 (25%)
- SRP (5%)
- PL. 7 & 12
- OJ
- EJ
- KJ (Lung)

Anti-Mi-2

Low specific

- low titer ← ANA < Speckled / Nucleolar
- Ss DNA
- Anti Ro
- PMSCL 70
- U1 RNP
- U2 RNP
- Ku

Autoantibody	Significance / Association
Anti-Mi2	. Classical DM (Most Specific), Responsive for ttt
. Anti Synthetases or Aminoacyl tRNA synthetases: . Anti-Jo-1 (histidyl) . PL-7, 12 (Thileny1) . EJ, OJ	→ Anti Synthetase Synd: – Raynaud's – Mechanic's Hand – Synovitis – ILD = (interstitial lung dse) – Resistant to ttt – Ø: Anti-aminoacyl tRNA synthetases.
. Anti 155KD/140 (TIF-1γ) (Transcriptional intermediary Factor)	. Mg ass. & Amyopathic DM
. Anti-NXP2 (Annexin XI)	. Juvenile DM.
. Anti CAMD 140	. CADM (clinically Amyopathic DM)
. Anti SRP (Signal Recogn. particle)	. Severe polymyositis (Fulminant) ē resistance to ttt & Cardiac & ILD
. PMSCL . U2RNP . KU	overlap ē scleroderma (sclerodermatomyositis)
. RO (SSA)	→ overlap ē, SCLE, Neonatal L.E

D Histopathology: (as SLE)

Treatment

(نتائج خاصة مع بعض) — Myositis → Cs; Dermatitis → as DLE; Calcinosis

Cut Manifs (difficult to be Treated)
↓
as DLE (Sunscreens + Topical Cs + Antimalarials) or Tacrolimus & MTX

NB resolve of Myopathy by Cs Not always ass. ē improvement Cut. Manifs.

[ttt of skin dis; 2012]

Myopathy → Cs (CPK اعلى)

- mild Cases (CPK < 1000 U/L) → Continous oral Cs (1mg/Kg/d) — أحسنه 50% عن 6 شهور كله على ٢-٣ سنوات
- severe Cases (> 1000 U/L) → . Continous > 1mg/Kg . Pulse or . Add other (Immunosuppressives)

THERAPEUTIC LADDER FOR DERMATOMYOSITIS	
Systemic therapy	(For Myopathy)
Oral prednisone	1 mg/kg tapered to 50% over 6 months and to zero over 2–3 years (1) option to use pulse, split-dose, or alternate-day (2) → mild cases
Methotrexate:	15 mg/m² weekly (2) → severe cases
Azathioprine:	2–3 mg/kg/day (3)
Others:	High-dose IVIg (2 g/kg/month) (1) – Pulse cyclophosphamide (0.5–1.0 g/m² monthly) (2) Chlorambucil (4 mg/day) (2) – Cyclosporine (3–5 mg/kg/day) (2) – Tacrolimus (0.12 mg/kg/day) (3) – Mycophenolate mofetil (1 g bid) (2) – Sirolimus (5 mg/day × 2 weeks, 2 mg/day × 2 weeks, then 1 mg/day) (3) Infliximab (5–10 mg/kg q 2 weeks initially) (3) Rituximab (375 mg/m²/infusion for 4 weekly infusions) (2) Plasmapheresis (3)*
Cutaneous lesions	
	Sunscreens (high solar protection factor including protection against UVA) (3) Topical corticosteroids (3) Hydroxychloroquine (200 mg bid; increased frequency of drug eruptions in patients with dermatomyositis) (2) Hydroxychloroquine (200 mg bid) plus quinacrine (100 mg/day) (3) Low-dose weekly methotrexate (5–15 mg weekly) (2) Retinoids (3) Topical tacrolimus (3)
Others:	Mycophenolate mofetil (3) Dapsone (3) Thalidomide (3)

Table 43.7 Therapeutic ladder for dermatomyositis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. *Double-blind trial showed no benefit.

CS
DLE, SCLE
- Sun protect
- Topical Cs
- Antimalarial
- Retinoids

Tt of Calcinosis Cutis:

(2C)
1 - Cs
2 - Probenicide
3 - Diltiazem
4 - Colchicine
5 - Surgical Excision

Types of Calcinosis cutis in DM

1. superficial cut.
2. periarticular S.C
3. along facial planes in ms
4. skeleton affection

Best ← Skin, S.C.T, muscle, Bone.

Table 43.5 -- Calculation of the skin severity index (DSSI).

CALCULATION OF THE DERMATOMYOSITIS SKIN SEVERITY INDEX (DSSI)	
Site of cutaneous involvement	Degree of involvement score 0, no involvement 1, <10% involvement 2, 10 to <30% involvement 3, 30 to <50% involvement 4, 50 to <70% involvement 5, 70 to <90% involvement 6, 90 to 100% involvement
Head (A *h*)	0 to 6
Trunk (A *t*)	0 to 6
Upper ext (A *u*)	0 to 6
Lower ext (A *l*)	0 to 6

Symptom/physical finding	Severity of involvement score 4, very severe	3, severe	2, moderate	1, slight	0, none
	Head (h)	*Trunk (t)*	*Upper ext (u)*	*Lower ext (l)*	
Redness (R)	0 to 4	0 to 4	0 to 4	0 to 4	
Induration (I)	0 to 4	0 to 4	0 to 4	0 to 4	
Scaliness (S)	0 to 4	0 to 4	0 to 4	0 to 4	

DSSI = 0.1(Ah)(Rh + Ih + Sh) + 0.3(At)(Rt + It + St) +0.2(Au)(Ru + Iu + Su) + 0.4(Al)(Rl + Il + Sl) = Total score (0–72)

Ext, extremity.

DIFFERENTIAL DIAGNOSIS OF DERMATOMYOSITIS
(1) **Systemic lupus erythematosus**
Physician might notice the nailfold telangiectasias and photodistributed poikiloderma but miss the muscle weakness, heliotrope, extensor distribution, and the violaceous hue (true lupus erythematosus might be present in the setting of an overlap syndrome)
(2) **Psoriasis**
Involvement of elbows and knees with papulosquamous lesions can lead to misdiagnosis
(3) **Airborne or allergic contact dermatitis**
Eyelid edema can be marked in dermatomyositis; look for additional sites of dermatitis
(4) **Photodrug eruption**
Photodistribution
(5) **Cutaneous T-cell lymphoma**
The poikiloderma often begins in intertriginous zones rather than on the scalp, face and extensor surfaces
(6) **Atopic dermatitis**
Usually in children, where the physician focuses on the pruritus and secondary eczematous changes
(7) **Scleroderma**
The nailfold telangiectasias are similar in appearance, but the dyspigmentation is quite different; edema of the hands is an early sign (true scleroderma may be present in the setting of an overlap syndrome)
(8) **Trichinosis**
Patients have painful muscles and periorbital edema, but not other features
(9) **Photodistributed form of multicentric reticulohistiocytosis**
Firm papules have distinct histologic features

Systemic Sclerosis

(Scleroderma)

Def: Autoimmune CT disease of unknow Etiology ch. by:

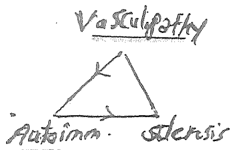
الترتيب مهم △

1. Raynaud's Phenomenon.
2. Cutaneous sclerosis (Hardening)
3. Systemic (internal) organs sclerosis

NB: the dis. has 3 Names:

- **SSc** — مش دقيق لأنه مش لازم يحدث فيه: Systemic = internal organ affect
- **Progressive SSc** — مش دقيق لانه "Not progressive"
- **Scleroderma** — الإسم الأصح.
  - Cutaneous (localized, circumscribed) → Morphea (patchy, asymm, No systemic affect of Rayn.)
  - Systemic (Bilat, symm ± ē systemic affect) → SSc

. Pathogenesis (see Morphea).



. Epidemiology:

- Age: 30-40 ys. (85% appear in 20-60 ys)
- Sex: M:F
  - Generally: 1:3-6
  - L SSc: 1:10
  - d SSc: 1:1

: Clinical presentat:

1. Clinical Picture →
2. Clinical Types
3. Criteria for D
4. DD.

C/P of SSC

Triad of:
- Raynauds
- Cut. sclerosis
- Systemic "

1. Raynaud's phenomenon:

def. Episodic vasospasm of digital arteries → Color changes ē expore to cold.

W → B → R

(White → Blue → Red) open of VS
VC — post cap ven open

LSSc: خ حالات تبعل قبل ال sclerosis بسنة أو عامين في نفس الوقت

dSSc: " " " " لسنوات عديدة

2. Cut. Sclerosis:

Has 3 phases (٣ مراحل)

- (A) Edematous phase: (stiff, puff fingers)
- (B) Indurative ": (Sclerotic) (Taut shiny, Hide board) — مشدود، جلد مدبوغ، حقيبة، waxy skin
- (C) Atrophic: (softened, burnt out).

Sclerotic skin appear:
- Smooth
- Firm
- Tight
- Shiny
- Yellow
- Hide board.

Site (مكان):
- LSSc: Acral — Face (90%), Hands ", Feet (10%)
- dSSc: Truncal (chest & proximal limbs) ± Acral.

- Other cut manifestations: Dyspigm — Calcinosis Cutis — Telangiect. Pruritis, Palmar Erythema, & ulcers.

(a) Dyspigmentation (50%)

Hyperpigm. (more common)

Diffuse Hyperpigm. (tanning) برونزي. Intensified over pressure areas as belt line & under brassiers.

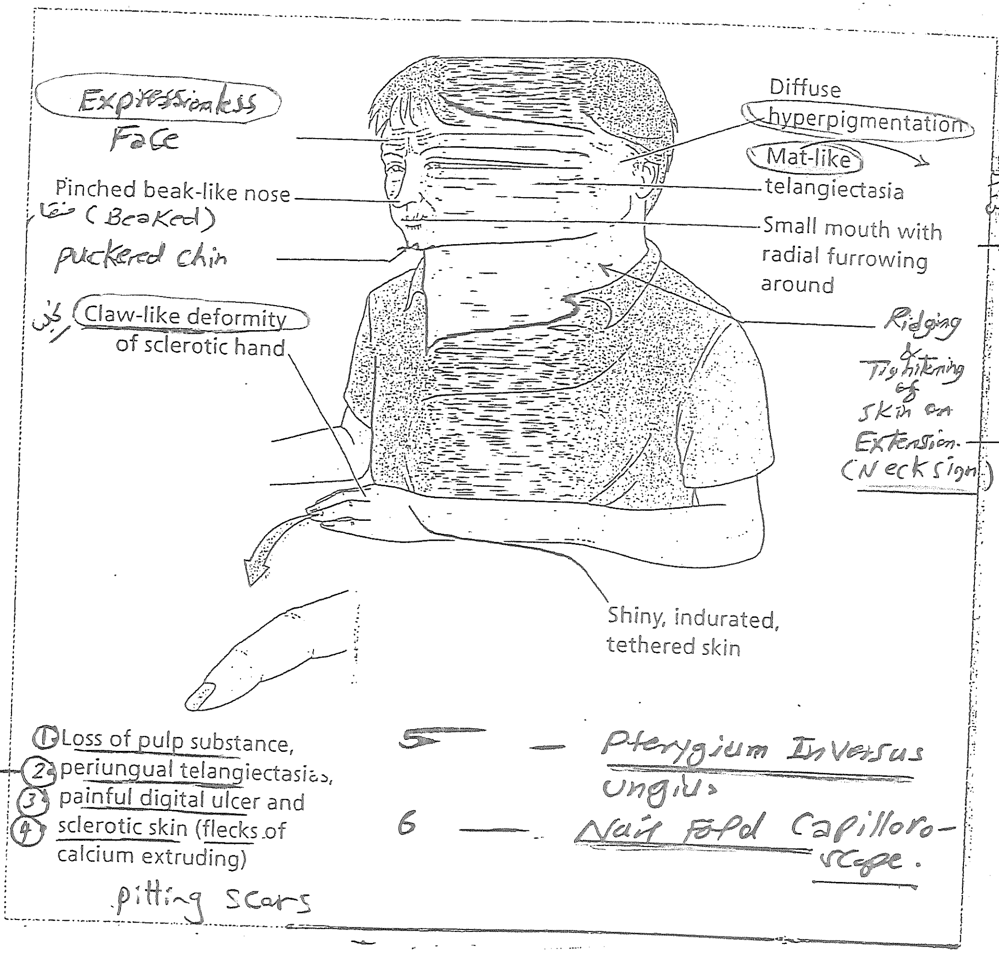
(Addison like Hyperpigm).

Hypopigm. (Leukoderma)

may affect NL or sclerotic skin of face & trunk → Leukoderma Except:

(Repigm vitiligo) → [a] Perifollicular areas: طبيعية
(very chic sign = Salt & Pepper sign)

[b] ± skin over superficial veins



NB
- Calcinosis Cu[tis] in SSc ch[...]
- Called: Thie[...] Weissenbach
- ± Ass. ē resor[ption] of bones of t[ermi]nal phalanges
ريش لحد الى ضيه والشن مع بعض

D) **Calcinosis Cutis:** as (DM)

- Usually at distal Joints.

(Dermatomyositis ē لا تعميم.)

E) **Telangiectasia** (75%) → Face, lips, Hands [discrete, Mats like]

- also: there may be:

(A) Ulcers:

- d.t → ischemi → at tips of digits
  → Fibrosis
  → Trauma → Interphalangial

- difficult ttt ⇐ may → movement limitat-, osteo[myelitis], Autoamputat- & depressi[on]

(B) Xerosis & pruritus

(C) palmar Erythema, P ⇒ Papular lesions d.t ← Lymph. obstruction, Amyeoid deposition, Fibrotic changes

(D) MM. affect-

3 Systemic (internal) organs Sclerosis

4 systems mainly involved by SSc:

1. Lung (die) → 2 Forms of the dis
2. Heart.
3. Kidney
4. GIT

onset: dSSc → ≃ 5 ys ; lSSc → > 5 ys

Interstitial Lung dis (ILD, 20٪)

- Alveolitis → Pulm. Fibrosis
- Diagnosis:
  1. Pulm. Function tests (PFTs).
  2. CT (High resolut~).
  3. Bronchoalveolar lavage

Pulm. HTN (PA

- Diagnosis:
  1. Echo.
  2. Rt sided Heart Catheterizat~

2 Heart

- Palpitat~.
- Friction Rubs.
- ~ CHF

3 Kidney - HTN

~ Renal Crisis.

- Accelerated HTN → RF
- Hemolytic anemia (Microangiopathic)

4 GIT

- Reflux & dysphagia.
- Constipat~
- diarrhea.
- Impaired peristalisis
- Int. Obst.
- malabsorption

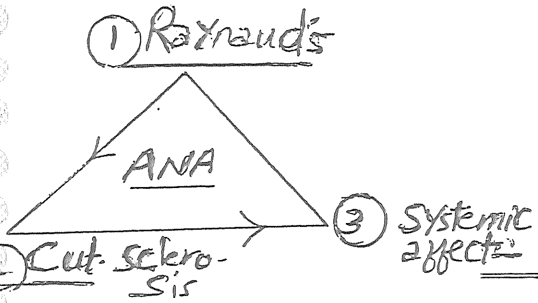
• Renal Crisis:

if SBP ↑ by (≥ 20) / DBP ↑ by (≥ 10) → From the baseline BP → Renal Crisis

2. Clinical Types:

1. LSSc (لوكيه) — LSSc (Acrosclerosis); CREST Synd. (ولا اسم قديم لـ lSSc)
2. d SSc
3. Transitory Form (LSSc / dSSc)
4. Pre SSc: full extent of sclerosis **Not** reached
5. Overlap SSc (DM or SLE)
6. SSc Sine Scleroderma: **No** Cut. affect
only systemic

ما تنساش المثلث ده



	LSSc (Acrosclerosis)	dSSc
Sex (M:F)	1 : 10	1 : 1
Raynaud's phenom.	occurs at same time (مع بعض) or precede the cut. sclerosis by ≃ 1 Y.	occurs many Ys (قبلها بكتير) before Cut. sclerosis.
Cut. Sclerosis	**Acral**	**Truncal** & ± Acral
Systemic affect^n	delayed affect^n (>5 Ys from onset of cut. sclerosis) (وقت طويل) More **PAH**	Early affect^n (within ≃ 5 Ys from onset of Cut sclerosis). More **ILD**
Nail fold Capilloscope (elongectasia)	dilatat^n without significant drop out.	Dilatation & **drop out** (destruct^n) ← يعمل Micro Hge
Autoanti-bodies	(الأساسي) - AntiCentromere (80%) (الأهم) - Anti Th/To - Anti U11/U12 RNP	- Anti-Topoisomerase I DNA (SCL70) & ("Bad prog" ILD ↑) - Anti-RNA Polymerase III (severe Cut, " renal, good progn) - also Antifibrillin (U3 RNP) (Myopathy, Cardio, PAH)
Course (10 Ys)	slowly progressive better prognosis Survival Rate **70%**	Rapid Progression Bad Prognosis Survival Rate: **20%**

NB The following ē lSSc > dSSc: Pulm. HTN; Sicca Synd.

Anti Centromere: lSSc 80%, dSSc 30%

Anti Scl70 (TopoIsomerase): LSSc 15, dSSc 60

ACR Criteria For SSc

A. Major Criteria : (1)

- Symmetric Cut. sclerosis proximal to MCP or MTP joints.

B. Minor Criteria : (3)

(i). Sclerodactyly (sclerosis of Fingers).

(ii). digital pitting scars (or) loss of substance from Finger Pad

(iii). Bibasilar pulm. Fibrosis.

- For Diagnosis : 1 Major [or] 2 minor.

NB ← What is the leading Cause of death in SSc ??

Was: Renal Crisis (but incid. ↓ ē use of ACEI)

Now: pulmonary affect ✓

SSc Autoantibodies (10) → ANA (98%)

LSSc
- Anti Centromere (PAH)
- Anti Th/To (Severe PAH & ILD)
- Anti U11/U12 RNP (Severe ILD)

dSSc
- Anti-Topoisomerase I (Bad Prog, ILD)
- Anti RNA Polymerase III (Better Prog) (Cut. Renal)
- Anti U3 RNP (Fibrillin)

Overlap
- Anti PM
- Anti-K (Both Myositis)
- Anti U1R

MCTD

CREST Synd. = LSSc

1. Calcinosis :. Calcific deposits at ← Extremities around joints ~ Bony prominences.
2. Raynaud's · Commonest : Flexors of Hands & extensors of elbow & knee (تكلس)
3. Esophageal dysmotility = lower Part → ↓ peristalsis
   - ↓ low Esoph. sph. Pressure
   - Incomplete Relaxation of LES = lower Esoph sphincter
4. sclerodactyly
5. Telangiectasia

(Site) dermal or (deeper)

Start at distal Fingers & progress proximally & may involve the Face.

- Rectangular or Elongated shape.
- Vs appear close to each other → discrete mats like. (Not as in osler Rendu Andrews 171)

⊙ Other Clinical Features : as in (LSSc.)

⊙ Autoantibodies : - ANA (Nucleolar).
- Anti Centromere (30%)
- others

⊙ Pathology : as lSSc

⊙ ~~HH~~ : ~ ~

DD of Morphea or SSC

"Morpheaform or Sclerodermoid Conditions"

(592)

DIFFERENTIAL DIAGNOSIS OF SCLERODERMOID CONDITIONS	
	Clinical features
Mucinoses	
Scleredema	Induration of the upper back, neck and face; occasional internal involvement (see Ch. 46)
Scleromyxedema	Waxy papules (often in a linear array); diffuse induration favoring the face, upper trunk, arms and thighs; monoclonal gammopathy; neurologic, gastrointestinal and pulmonary involvement (see Ch. 46)
Immunologic	
Chronic GVHD*	Morpheaform plaques favoring the trunk, which may become generalized; eosinophilic fasciitis (see Ch. 12)
Eosinophilic fasciitis	Symmetric induration with a 'pseudo-cellulite' appearance on the extremities (sparing hands and feet) (see text)
Generalized morphea*	Expansion and coalescence of morphea plaques to involve a large portion of the trunk and extremities (see Ch. 96)
Fibroblastic rheumatism	Sclerodactyly; fibrotic nodules on the hands
Paraneoplastic	
POEMS syndrome	Sclerotic skin on the extremities (see Ch. 114)
Amyloidosis (primary systemic)†	Diffuse induration favoring the face, distal extremities and trunk (see Ch. 47)
Carcinoid syndrome	Sclerotic skin on the legs (see Table 52.3)
Neoplastic	
Carcinoma *en cuirasse**	Sclerodermoid encasement of the chest by metastatic carcinoma (usually breast cancer)
Metabolic	
Diabetic cheiroarthropathy	Thickened skin and limited mobility of the hands (see Table 52.4)
Porphyria cutanea tarda*,‡	Morpheaform plaques in sun-exposed areas (see Chs 49 & 96)
Neurologic	
Reflex sympathetic dystrophy*	Painful, cold, swollen extremity eventually develops cutaneous sclerosis (see Ch. 7)
Spinal cord injury	Sclerotic skin in affected areas
Toxin-mediated	
Nephrogenic systemic fibrosis*	Associated with exposure to gadolinium-based contrast agents (US, 1997-present; now worldwide) (see text)
Eosinophilia-myalgia syndrome	Associated with L-tryptophan ingestion (US, 1989) (see text)
Toxic oil syndrome*	Associated with toxic oil ingestion (Spain, 1981) (see text)
Drug- or chemical-induced (see text)	
Bleomycin*	Acrosclerosis, Raynaud's phenomenon; pulmonary fibrosis (more common, usually no concurrent skin lesions)
Taxanes	Edema followed by sclerosis of the lower extremities; acrosclerosis
Vinyl chloride, chlorinated hydrocarbons*	Acrosclerosis, acral fibrotic papulonodules, Raynaud's phenomenon, acro-osteolysis; pulmonary fibrosis
Venous insufficiency	
Lipodermatosclerosis*	Woody induration and hemosiderin pigmentation on the lower legs; may also involve the pannus (see Ch. 100)
Genetic disorders	
Restrictive dermopathy§	Tight, thin skin over the entire body; joint contractures; *LMNA* or *ZMPSTE24* mutations
Hutchinson-Gilford progeria	Sclerotic skin on the lower trunk, buttocks and thighs; *LMNA* mutations (see Ch. 62)
Werner syndrome	Tight, sclerotic skin on the distal extremities; *RECQL2* mutations (see Ch. 62)
Stiff skin syndrome*	Fibrosis of the skin/fascia of the buttocks and thighs with hip contractures (see text)
Phenylketonuria	Sclerotic skin on the thighs and buttocks with hip contractures (see Ch. 62)
Winchester syndrome*	Diffuse, symmetric, leathery skin thickening; fibrotic plaques or bands; *MMP2* mutations (see Table 69.2)
Ataxia telangiectasia	Tight, sclerotic facial skin (see Ch. 59)
Muriez syndrome	Sclerodactyly; atrophic skin on dorsal surfaces of hands and feet; palmoplantar keratoderma (see Ch. 57)

*Can overlap with morpheaform disorders, which are listed in Table 96.1.
†Primary cutaneous amyloidosis can also occur in patients with systemic sclerosis and generalized morphea.
‡May also be observed in patients with congenital erythropoietic porphyria and hepatoerythropoietic porphyria.
§Sclerodermoid changes are typically present at birth.

H-Synd

Table 44.6 Differential diagnosis of sclerodermoid conditions.

③
- Scleroderma
- Scleromyxedema
- Scleroma Neonat

④
- Shulman synd
- Stiff skin "
- Nephrogenic systemic fibrosis

L.T.P →
- Toxic oil synd
- Eosinophilic Myalgia synd

- PCT
- GVHD
- PKU
- Lipodermato-sclerosis

- Amyloidosis
- PoEMS
- Carcinoid Synd
- Carcinoma en Cuirasse
- Werne- & H Gilf
- Ataxia Telang

- DM Cheiro athropathy
- Rh fibroblastic
- Synds ⑥ with
- Drugs
  - Vit K
  - Vit B
  - Bleomycin
  - Taxanes
  - Hydrocarb

Scleroderma Related disorders.

1. Eosinophilic fasciitis
2. Stiff skin synd.
3. Nephrogenic systemic fibrosis
4. Eosinophilic Myalgia Synd.

1. Eosinophilic Fasciitis (Shulman's Synd.): See Morphea.

2. Stiff Skin Synd.

- Age: Cong. or Early childhood. (fibrillin gene Mutat=)
- Clp: Rock hard induration & thickening of skin & S.C.T mainly affecting buttocks & thighs with chic sparing of inguinal Area (Folds) - X
  X - Hands & Feet are spared.
  Spar
- Ass: (a) Hypertrichosis
  (b) chic posture of Hip & Knee flexion (Joint restrict=) ∴ prominent lumbar lordosis while standing
- Course: → stable or slowly progressive. (without)
  XX Int. organ affection.
- Path: Thickened, Hyalinized (fascia) without an ass. inflamm. infiltrate X
  Dermis: ± Mucin & Collagen Hyalinizat=
- ttt → (No) effective ttt
  → physiotherapy → ↓ Joint Contracture.

سؤال امتحان Q

Eosinophilic fasciitis = Shulman synd.

Def: Acute onset of fasciitis —Followed BY→ Indurat° similar to that of Morphea (+) Eosinophilia. scleroder moid picture

. Epidemiology:

- Age: 30-60 ys.
- Sex: M=F

after severe physical activity

. Aet. unknown but ± d.t: Inf. (Borr) - drugs (Atorv.) - Autoimmune (ANA) - oth.

1. Autoimmune → d.t ass. ANA & Hypogammag. ↑ γ globulin
2. Enviromental → drugs (Atorvastatin), Toxins & Radiation
3. Infection: Borrelia Burgdorferi
4. others: ↑ TGFB, ↑ IL5, CD8, ↑ Mangenese SOD & Tissue inhibitor of Metalo proteinas (TMP1) (Marker of dis.)

. C/P. 3d. following sterneous physical activity

* clinically 3 stages:

1. 1st → Bilat, symm, diff. Erythema & Tenderness. (erythema)
2. 2nd (oedematous ph.): "dimpled appearance" (edema) — Coarse (Cobblestony) or fine (Peau d'orange) → "Pseudo-cellulite"
3. 3rd: rippling, Indurat°, fibrosis, Hypopigm (Woody skin) (woody skin)

NB: Ass. ① Joint contracture & fibrosis ② Arthritis ③ Myositis ④ Neuropathy ⑤ Carpal Tunel

البعض يعتبرها نوع من الـ Morphea & الآخرين: كيان منفصل

. pathology: Fascial fibrosis (fascia thickened (10-50) times NL), Dermal Fibrosis c̄ fascial & subfascial ms Infilt.

. Diagnosis. - Fascial Biopsy & MRI
- ↑ ESR & Eosinophils.

Treatment

1. CS لازم نبدأ بها بس على مدار سنة
2. others NSAIDs, MTX, PUVA-

NEPHROGENIC SYSTEMIC FIBROSIS (NEPHROGENIC FIBROSING DERMOPATHY)

- def.: Sclerodermoid condition usually affecting RF patient
- Epidemiology:
  - Age: any but common in middle aged.
  - sex: M = F.
  - Risky patients:
    1- Renal impairment: sp. CRF with dialysis
    2- chr. LCF.
    3- HyperCoagulable states.
    4- Surgical procedure
    5- IV dye (gadolinium)
- Pathogenesis: → Aberrant targeting of Circulating Fibrocytes to peripheral tissues ↓ (BM derived WBC).
- CIP → Bilat., Symm., Erythematous - Hyperpigmented plaques on Extremities & Trunk with irregular advancing edge (Amebotid appearance)..
  - Ass: ① Joint contracture
    ② Yellow scleral plaques
    ③ systemic fibrosis of "Heart, Lung, ms."
- Pathology: - Haphazardly arranged Collagen bandles
  - ↑Mucin deposit
  - ↑ fibroblast cells that stains +ve for CD34 & ProCollagen I
  - (±) Gadolinium particles (by spectroscopy)

Refractory ← ## → 1- Renal Transplant
2- Immunosuppp.
3- PDT 4- pharesis 5- IVIG 6- UVA1

Antimalarials (مهم)

Mech.

1. Immunomodulating
   - ↓ IL2 product
   - ↓ MHC expression by macrophages.
2. Antiinflammatory
3. Antiplatelet (so used in APS).
4. Photoprotection (in PCT) → In PCT chelate porphyrin

3:
- Chloroquine → 250 mg (Dagrinol)®, Alexoquine®
- Hydroxy Chloroquine → 200 mg plaquenil® & Hydroquine
- Quinacrine → Atabrine 100 mg®

Kinetics:
- Metabolized by liver
- 50% Excreted via kidney
- Half life 50 ds (slowly released → delayed onset of effect ē in 3-4 ms (or 6-8 ws)

Indications:
1. LE (other AICTD) الاهم — "مرة" ← بتقيم عند الزرقة ← ممكن ب p.m شيبه وما
2. PMLE
3. others: L.P, GVHD, PCT, GA, Scarcoidosis, DM & APS.

S.E:

1. Common:
"Pigmentary"
- ↓ (i) Hyperpigm. of Hair
- ↑↑ (ii) Q & HQ → Blue-Black pigm of: skin, MM (Hard palate) Nail, sclera & Cartilage.
- (iii) Atebrine: yellow pigm. of skin & Conjunctiva

2. Uncommon
- (i). NV → Nausea, Vomiting
- (ii). Hepatotoxicity
- (iii). Irritability

3. Rare
- (i) Retinopathy — بيتركز ← Choroid ← مهم ← أكثر ميلانين
  - * Visual field defe[ct] to red objects & " paracentral scotom[a]
  - * Q > HQ. Atebrine has No ocular SE
  - * Early reversible later Non reversible
- (ii) CBC: Hemolytic anemia in G6PD defient pts. ← "ē Non-dermatological Antimalarial" "مهم"
- (iii) others
  - PS. (↑↑)
  - Rash & FDE
  - EM

NB to ↓↓ ocular S.E

1. Sunglasses
2. Eye Exam / 6ms
3. Stop after 6ms or at winter
4. ↓ dose after improvement ± Atebrine

- C.I: ① Hypersensitivity
② Impaired liver
③. BM --
④. Retinopathy

- preg. & Lactat
Category C

(American Acad. of Ped.)

- Interact: 1- Cimetidin → ↑ level

تفاعلات دوائية → 2- Kaolin & Mg Trisilicat: ↓ Abs

3- Q & HQ should be avoided but Atebrine may be combined

يقلل مفعولها كثير 4- Smoking. يطل زاد

- Dosage (½ - 1 مرة)

1- Q → 125-250 mg 1d (or 3.5-4 mg/kg/d)

2- HQ → 200-400 mg 1d (or 6.5 mg/kg/d)
(1-2 مرة)

3- Atebrine. 100 mg 1d.

4- In PCT مع الدم . Q: 125 mg twice/w مرتين
HQ: 100 mg Trice/w ٣ مرات

Treatment of SSc

1. ## of Raynaud's (See below)

2. ## of Sclerosis: (usually (Non) effective) → Antifibrotics:

- D-penicillamine.
- Colchicine.
- Griseofulvin
- Trental
- MTX
- IFN (α & γ)
- cyclosph.
- Phototherapy. → (UVA1)
- photopharesis.
- Tyrosine Kinase Inhibitors: (Imatinib.) (TKI)

3. ## of ulcers:-

- ## of Raynaud's
- Minimal Mechanical debridement
- Moist occlusive dressing (Hydrocolloid)
- Topicals: Collagenase, PDGF

4. ## of Calcinosis Cutis:

(3C)
- Cs
- Colchicine
- CCB

- Warfarin
- probencid
- Deltiazem

- Alum - hydroxide
- surgical

5. ## of Complicat:

(PAH) - Pulm. HTN → O2 & Anticoagulant; Epoprostenol (PG) & Sildenafil & Bosentan (Endothelin Rs)

(ILD) - pulm. Fibrosis → Cyclophosphamide. ↓ (Cs + MM)

- Renal Crisis → ACEI
- Reflux osoph. → Proton pump inhibitors. PPI; promotility Agents (ondansetron)

(أساسي) **Mixed Connective Tissue dis. (MCTD)**

: EM Bip. (2004)

(MCTD = Mixture ...)

. def disorder in ⓦ features of many CTDs — doesnot fullfill criteria of one of them

as
- SLE
- SSc
- DM
- SS

Can co-exist & overlap

> . Considered as a distinct synd. ē specific serology & shouldnt be confused ē "overlap synd" in ⓦ there is combinat^n of diseases where each complies ē diagn. criteria for that disorder

. Ch By : [1] Course → - chr. & milder than other CTDs.

مرحلة ع النص بينهم - Considered as intermediate stage

ثم يتحول لمرض واحد منهم & evantually becomes either (SLE) or (SSc)

(احفظ لعيـن جدا) → [2] Specific Marker → Anti U1-RNP

. AEt : unknown but ± ass ē:

1- HLA DR4 (مهم)
2- Genetic predisposit^n.

> . D : . ANA (speckled) . Anti U1 RNP
> . Rx : كالعادة

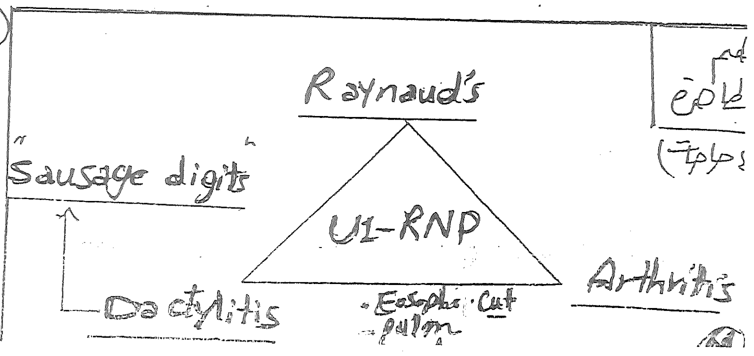
. Age : [30-50 Ys] (in children course ± severe ē ↑ incid of — Heart, Kidney, Thrombocytop.)

. Sex : M : F = [1 : 4.]

. C/P

- . Raynaud's phenomenon → Most common presentat^n & first to appear.
- . Arthralgia / Arthritis
- Esophageal Hypomotility
- Pulm. dysf. (Pulm. HTN)
- Renal → 5%
- . Swollen Hands
- . Myositis
- . Rash — Vasculitis, DLE, Alopecia, Erythema, Heliotrope E, Gottron's
- . Leukopenia

(Never Sclero-dactyly)



Sjogren's Synd (sicca ~ Mikulicz dis.)

def Autoimmune dis. That affects primarily secretory glands sp < lacrimal / salivary & has classical Δ of:

- KCS.
- Xerostomia.
- Arthritis

others
(i) Cut.
(ii) systemic

NB. Has mucocut manifs that may be the first presenting signs.

@ may be the 1ry or Ass. ē < R.A (+++) / SLE, scLE / SSc / MCTDs

3 Types
- 1ry
- 2ry
- Juvenile

CIP: European Community Criteria For Dx of SS:

eye & tongue:
- Xerophthalmia.
- Xerostomia.
- Corneal damage

Salivary:
- Impaired salivary gland funct~.
- Salivary gland Lymphocytic infilt.
- +ve Autoantibodies (Anti Ro (SSA) & Anti La (SSB))

Age: any but common in 30-50

Sex: M:F 1:9

التشخيص بالمختبر (+) Anti alpha fodrin Ab

① - Xerophthalmia:-

- (KCS) or dry eye Synd ch BY chronic dryness of Cornea & conjunctiva.
- Discomfort (redness, burning, itching & FB sensat~).

الفم

2 - Xerostomia:

- Dryness.
- Tongue: → Red, smooth & dry
  - Dental Caries
  - oral Candidiasis
  - perteche
- 3 glands ← Parotid & sumb mandibular & maxillary gland Enlargement.

3 - Other mm:

- Atrophic changes of
  - URT → Nasal dryness & Inf.
  - Atrophic Rhinitis
  - Vulva & vagina → Vaginitis.
  - Anal & Rectal → pruritus & Inflamm.

4 - Cut. Manifs

- Dryness <
  - Dryness & Xerosis → pruritus.
  - Dryness of Hair → brittle, Fragile & generalized Alopecia.
- Erythema <
- Vasculitis L.L
- Alopecia

- Erythema of Nose & cheeks
- Vasculitis (post capillary Venules of L.L)
- Erythema / Nodule plaques
  - Sweet synd. like annular Ery.
  - SCLE like
  - Papular Erythema

H Consecutive immunology

Serology

- Anti α fodrin (70%)
- Anti Ro (SSA) (60%)
- Anti La (SSB) (20%)

5 - Extraglandular manifs:

1. GIT
- E. dys
- HSM
- AbN oesoph. motility
- splenomegaly
- Pancreatic affect
- Hepatitis

2. Lung
- Pulm
  - Fibrosis
  - HTN
  - Inf.

3. UT
- irritated UB
- Frequency
- Nephritis
- RT. Acidosis

4. CNS

5. Arthritis

Antiphospholipid Syndrome (2012) (2014)
(APS)

Def. AutoImmune disorder ch. By Triad of: △

[1] Thrombosis:
* (≥1) arterial, venous or small Vs Thrombosis in any organ confirmed by doppler or HP.

لما يخليك تشك
- Age < ♂ <55 / ♀ <65
- ē No risk factor
- ē Attack of
  - stroke
  - MI
  - DVT
  - p Embolism
  - Adrenal Hge.

* Affected organs (±) Cerebral, Cardiac, pulm., Adrenal, ocular, Musculosk. & peripheral.

[2] pregnancy Morbidity:
- Early abort. < 10ws. (≥ 3) Consecutive, Spontaneous, unexplain
- Late abort. > 10ws: (≥ 1) Spontaneous abort.
- preterm labour ≤ 34ws: because of
  - Eclampsia
  - preclampsia
  - placental insuff

[3] Autoantibodies ≥1
- Anti-Cardiolipin / phospholipid (aCL): IgG > IgM (أفضل)
- Lupus Anticoagulant ab (LA) → (بيعاد مرتين فرق بينهم ١٢ أسبوع)
- Anti-β2 Glycoprotein I.

For Ø = 1 lab + 1 Clinical

other

• Manifestat.s

1- **Cut.**
- Livedo Reticularis (80%) (٢٨)
- Leg ulcers
- (4A)
  - Atrophaie blanche
  - Acrocyanosis
  - Anetoderm
  - Alopecia
- Raynaud's
- Thrombophlebitis
- Vasculitis
- Blue-Toe synd.

2- **Neuro**: migraine, Seizures, Multi-infarct dementia.

3- **CVS**: Murmur, Valvular Vegetations.

4- **Blood**: Hemolytic anemia & thrombocytopenia

• Lab. InVs
- APTT
- False +ve serology of $
- CBC

2 Varieties of APS

(1) **Seronegative AP (like) synd.:** The same clinical Manifs but (−ve IAVs)

(2) **Catastrophic APS:** Severe, progressive with multiple Vs affect; **fatal within few days.** (TTT: IVIG, Cs, Rituximab)

Etiopathogenesis: There are 2 Types of APS:

- **1ry APS** (Not ass. ē any underlying dis.)
- **2ry APS** (± ass. ē systemic illness):
  - (i). **AICDs**: SLE, SSc, MCTDs & RA. (& ± BD)
  - (ii). **Infect**: HCV, HIV, $, Malaria
  - (iii). **Drugs**:
    - Cardiac: BB, Hydralazine, Procainam
    - Neurological: phenytoin
    - Others: "Amoxicillin" & IFN-α.

- on Both Types there are product of Many **autoabs** → Thrombosis → placental affect → pregnancy Morbidity.
- these antibodies Include:
  1. **ACL abs** (Antiphospholipid): against memb. phospholipids.
  2. **A B2 Glycoprotein I:** plasma protein associating memb. phospholipid
  3. **LA. Abs** (misnomer Not related to lupus Nor No Coagulat but theres Thrombosis): Abs against Coagulat factors (Prothrombin, protein C & S, Annexins, LDL → atherosclerosis & MI).
  4. **defective platelet & endothelium of BVs**

pregnant ē HX of loss . Heparine + Aspirin (Both) prenatal & post partum then Warfarin

• TTT of APS (No specific ttt)

1ry thromboprophylaxis

. **prophylactic** (ttt عوامل الخطر)

1. **General step** < Smoking / ocps ; ttt < HTN / Hyperlipidemia (statins)
2. **Aspirin** (?) lowdose) or **Clopedogrel** (if Allergic to Aspirin)
3. **Hydroxy chloroquine**: APS ass. ē SLE (Antithrombotic effect)

2ry thromboprophylaxis

. **Thrombosis:** IV or S.C Heparin —then→ Warfarin (**adjust** < Venous INR 2-3 / Arterial 3) (For l

Allergy to Warfarin: Newer Agents Antithrombin & Factor X, Rituximab.

Raynaud's phenomenon (EM, Bologna, D.N).

Def: Vaso spastic dis. ch^ By Episodic Reduction of Blood Supply to the Fingers & /or Toes mainly in Response to Cold Exposure.

C/P: ⊙ Affected fingers or Toes show at least 3 Color changes:

بنفس الترتيب (W, B, R)
- White (Pallor)
- Blue (Cyanosis) [↓Flow]
- Red (Hyperemia) [↑ Flow]

} usually reversible

⊙ There are may be:
- Pain / Numbness
- digital ulcers.
- other CTD manifestation

- **Types of Raynaud's ph.:**

① **1ry Raynaud's ph.:** (Raynaud's dis.) أو
- Common, Younger girls
- No any underlying Medical Problem.

② **2ry Raynaud's Ph.:** uncommon & occurs in associat^ with other problem specially SSc

أسباب - **Conditions Ass. with Raynaud's Phenomenon** (2ry Rayn.)

1 AI-CTDs:
- Scleroderma (SSc)
- SLE
- MCTDs
- DM/PM
- RA
- SS

2 Inf.
- HBV
- HCV (sp. ass. ē mixed ⊙ Type III Cryoglob.)
- Mycoplasma (ē Cold Agglutinins)

3. Neoplastic:

- Leukemia
- lymphoma
- MM
- Carcinoma
- Polycythemia
- Type I Cryoglobulinemia

4. Environmental:

- Vibral injury
- Frostbite
- lead & Arsenic exposure
- Smoking.

eg →

5. Metabolic / Endocrinal:

- DM
- Acromegaly
- Myxoedema
- Pheochromocytoma
- Fabry's dis.

6. Hematological:

- PCRV.
- PCH.
- Cryofibringenemia
- Cryoglobulinemia.

7. Drug.

- CPs.
- BB.
- CyA.
- Bromocriptine
- Ergot Alkaloids

8. Syndromes:

- Carpel tunnel
- Thoracic outlet

← paraneoplastic Acral vascular synd.

- Asthetosclerosis
- Vasculitis ←
- Acrocyanosis ←

← livedo Retic.
chilblains.

How to differentiate bet 2 Types of Raynaud's.

	1ry Raynaud's (Rayn. dis.)	2ry Raynaud's
• Incid	• More Common	• less Common.
• Sex: M:F	1 : 20	1 : 4.
Age:	< 25 ys	> 25 ys.
• Ppt. of Attacks	Cold, Emotional stress	Cold
NO of " :	< 5 / d. (Bilat. & symm.)	> 5 / d (Asymm., ≥ 1 digits ± affected)
Ischemic Injury	(good prognosis)	present (Bad prog.)
AbNL Capillroscope		" pitting scars; dilitation dropout > dermoscope
• ANA	Absent. (-ve)	+ve (> 90%)
• Anticentromere		+ve (30%)
• Anti SCL 70		+ve (70%)
• Platelet activat^ (invivo)		+ve (90%)

(ttt)

① General Measures:

A – Avoid Smoking & Drugs as BB

B – Avoid Cold & Emotional Stress.

C – Abort of attack → whirling [illegible] arm (Soft ball pitch) maneuver: arm swinging 360° circle → restore circ SSc.

② Specific ttt

• 2ry Raynaud's → ttt of underlying (AEt)

• 1ry "

→ • CCB → اضراباى ↓BP — epilate 20-60 mg

→ • ACEI **

• PGs

• Sildenafil

Cut. Manifs of Rheumatoid Arthritis (RA)

[illegible]

Non-specific (General)

- Skin
  - pale
  - Atrophic
  - Fragile → Easy bruising
  - palmar Erythema
- Nails: Brittle

Specific

1. Palisading granulomas
   - Rh. Nodu[les]
   - GD
2. Neutrophilic dermatoses.
3. Vascular
4. Cut. manifs of
   - Felty's
   - Still's d[isease]
5. Drug Related.

---

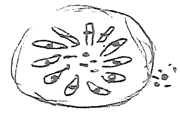
(1) Rh. Nodules

- Most Common Cut. Manifs.
- Ass. ē High or Mod. titer ↑ RF & usually at (late) stage of dis[ease] [illegible] Arthritis

→ Asympt., firm, Semimobile (Nodules) at extensor surfaces
- of Joints e.g Fingers, Heel, forearm, back, scapula, Sacrum [illegible]
- Can affect Visceral organs (lung, Heart, ms).

- if it appears in large No after MTX ℞ → (MTX induced Accelerated R. Nodulosis) عددها

Path
- Central Zone: Eos, Fibrin & Cell. Hyalinizat
- Mid Zone: palisaded Histiocytes.
- peripheral Zone: Vascular CT & mixed infilt.



NB Rh. Nodules like lesions + -Ve RF → S.C GA (PseudoRh. Nodules) or Any other palisading granuloma. ([illegible] RF in ↑ titer)

℞
- Surgical Excision
- ILs ([illegible])

Differences from the subcutaneous nodules of rheumatic fever include more fibrinoid maternal, little cellular infiltrate and minimal zoning and fibrosis in rheumatic nodules. Nodules from patients with still's disease resemble histologically those of rheumatic fever.

GD (Granulomatous Dermatitis)

Interstitial GD (IGD)

C/P. Annular or linear (Rope sign) Erythematous plaques at lat.
- Trunk, Thighs, buttocks & Axilla
- occur in Both ← RA or Sero-ve Arthritis

HP. Rosettes of Palisading Histocytes surrounding foci of Degenerated collagen

DD: Patch GA, leprosy, morphea

Palisaded Neut. GD (PNGD)

Psoriasiform lesion

- Crusted, umbilicated Papulonodules at Elbow or dorsal Hands
- Ass: Rh. sLE, ANCA +ve Vasculitis (Churg Strauss)

Neutrophilic infil. & foci of LCV or as IGD

- Rh. Nodules, Papular GA

Drug induced GD

- ACEI
- CCB & BB
- Statins

(Rapid onset)

CIP erythem. vidu... Pap., Nods & Plaques ... Flexures & thighs ... ↓ of ... GD

- ILCs
- Dapsone.
- HP: Interstitial Histiocytes ... Variable → degen. elastic fib.

(2) Rheumatoid Vascular lesions (4)

- Vasculitis
- Capillaritis
- Barwaters Histiocytosis

(i) Vasculitis ← Cut. (کیوٹی) / ocular / systemic

(ii) Baywaters Nodules.

- CIP, small, painful, purpuric Nodules at pulps of digits
- Path. SVV & (No) systemic affect.

(iii) Capillaritis (pigmented purpuric Dermatosis)

(iv) Intravascular / Intralymphatic Histiocytosis.

(Erythema, Indurat, papules over swollen joint sp. Elbow).

(3) Neutrophilic dermatoses: [PG, Sweet]

- Rh. Neutrophilic [Dermatitis, Panniculitis]

(i) PG

(ii) Sweet's synd.

(iii) Rheum. Neutrophilic dermatitis: (Neutr. Vascular react.)

- Bilat. asympt. persistant Erythm Nodules & plaques that may ulcerate at Extensor Forearm & Hands. (urticarial like)
- Hist. & Clinically: as sweets (diffuse dermal Neut. infilt. & Papillary Microabscess)

DD ← sweet urticarial like → DD

DD of Sweet:
- (i) No ← Tenderness / Systemic manifs
- (ii) Site.

(vi) Rheum. Neutrophilic Panniculitis: Panniculitis Nodules of L.L → ulcerat & drainage.

④ Cut. Manifs of:

(i) Felty's Synd: Severe subtype of RA

Ch BY Δ of:
1- RA.
2- Neutropenia
3- Splenomegaly +
- Leg ulcers (PG like)

(ii) Still's dis: Juvenile Idiopathic (Rheum) Arthritis.

2 Types: Systemic onset (SOJIA) (<16y/M
Adult onset (AOJIA) (20-40, F

· CIP

Systemic
- Spiking fever
- Rash.
- Sore throat
- Arthralgia
- L.N
- HSM

Cut.
(i). Asympt, Evanescent, ± linear macules, papules & plaques at pressure or Trauma sites.
(ii) periorbital Edema
(iii) linear, persistent, pruritic, Violaceous papules & Nodules (L.p like)
(less common)

Lab
- leukocytosis
- Anemia
- ↑ ESR / CRP
- ↑ Ferritin.
- +ve ANA
- -ve RF.

⑤ Complications of Therapy.

(i). NSAIDs → Pseudoporphyria & TEN

(ii) MTX → MTx Induced Accelerated Rheum- Nodulosis (at Hands)

(iii) TNF Inhibitors
- React at site of infect
- Urticaria & Vasculitis
- GD
- pp Pustulosis

Dif

· What's ??
- Rheum. Nodules
- // Nodulosis
- Rh. papules ?? (PNGD)

Scleroderma = Sclerosis

Def. Chr., Idiopathic, Inflammatory disorder that may affect the skin &/or systemic organs & ch' By "sclerosis"

(Excessive Collag deposit + ↓ No of Fibroblast)

- It includes: (Sclerosing skin disorders)
  1. Morphea
  2. SSc → See CTDs
  3. LS → See lichenoid dermatoses.
  4. Morphea-form / Sclerodermoid disorders.

⊙ NB: Fibrosis: ↑↑ Collag & ↓N Fibroblast

Morphea & SSc.

Localized / Cut Scleroderma (Morphea)

* ch' By:
- Patchy, Asymm. (- Limb)
- No Sclerodactyly
- No Raynaud's
- No Systemic affect
- NL Nail fold capillaroscopy.

* Types:

1. Plaque (Circumscribed) Morphea
   - classical
   - Guttate
   - Nodular (Keloid)
   - Bullous
   - APP.
2. Generalized Morphea.
3. Linear Morphea: (Face, limbs)
   - Linear M. of Limbs
   - en Cup de Sabre (face)
   - Parry-Romberg syn.
4. Deep Morphea (pansclerotic M = Morphea Profunda)
5. Mixed Type.

2 diffuse = Systemic (SSc = Scleroderma)

ch' By:
- diffuse, Symm.
- Sclerodactyly
- Raynaud's
- systemic affect (±) (Int. organs)
- Ab NL Nailfold Capillaroscopy.

2 Types: lSSc / dSSc

- NB Morphea According to the Depth of Sclerosis:
  1. Superficial (Dermal): Circumscribed plaque & Generalized
  2. Deep
     1. deep dermis, S.C.T, fascia, ms, Bones, Meninges & Brain → Linear Type.
     2. M-profunda: S.C.T & fascia

Pathogenesis of Scleroderma

Triggers → Triad ← Vasculopathy, Autoimmunity, Fibrosis or sclerosis

SSc

- Genetics: HLA B8 & DR3
- Cosmetics: silicone
- Solvents: Benzene
- Free Radicals.
- Drugs ← Vit K & B, DP ✓, Cocaine.

Morphea

- Genetics: in M. profunda.
- Trauma
- Vaccination
- Infection: Borrelia Burgdorferi
- Radiotherapy

↓

1- Vascular Injury (Very early):

- Micro vascular injury of endothel of capillaries →
  - ② Endothelial changes ← Swelling, Thickened (reduplication), Hyperplasia
  - ⑥ ↑ Endothelial cell markers
    - E1
    - sVCAMs
    - sE-selectin
    - VEGF

this Injury → Hypoxia

2- Auto Immunity

CD4 → differentiation → Th2 → IL4, TGF-β → ++ Fibroblast → Excessive Collagen (Sclerosis)

Others: Borrelia Burgdorferi → Penicillin

3- Excessive Collagen deposit (I, III, V, VII) also other EC matrix

- Fibronectin
- proteoglycans

Triggers → Vascular injury → Hypoxia → Autoimmunity → Excessive Collagen deposit

Morphea (see Pathogenesis & Classificat...

(Localized or cut. scleroderma)

- Epidemiology
  - M > F
  - Age (usually < 18 Ys)
- Types:

① Plaque Type:

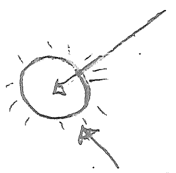
- Size of Lesion: 2 - 15 cm
- Site: asymm. on Trunk
- ___ : 3 stages

[1] Oedematous stage:

- Edematous, Indurated, Erythematous or Violaceous plaques.

[2] Sclerotic stage: lesions show:

- Smooth
- Ivory white
- Waxy
- Sclerotic
- XX — lost < Follicle, Sweat glands
- ± PIH → [post inflam hyperpig]



- ⊙ Center: Sclerotic (Hard), Smooth, Ivory Waxy, white with loss of Follicles & Sweat glands.
- ⊙ Edge: Active, advancing shows Erythem-Violaceous Color & Telangiectasia

Improve ē ttt — active ← ليلاك = (Lilac-ring) حلق (ع[illegible]

[3] Atrophic Stage: (after ms – Ys): skin softening ē Dermal Atrophy (50%)

NB: Postinflamm. Hyperpigm.: may demonates over sclerotic lesions & envolute after sometime.
↓
Non active — Not improve ē ttt

Variants of Plaque Morphea:

① Guttate: Multiple, small, chalk-White lesions without Induration (d.t superficial pathology)

- Both diseases Called: "White spot diseases."
  1. Guttate Morphea
  2. LSA
  3. IGH
  4. Guttate Vitiligo
  5. Arsenic
  6. Guttate PS

- D.D: LSA but there are NO:
  - Epid. Atrophy
  - Follicular plugging.

② Nodular (Keloid): Keloid like nodules or streaks in presence of Typical plaque like Morphea. (usually: indistinguishable from Keloids)

③ Bullous: subepid. bullae on Top of Morphea lesions. (d.t stasis of lymphatic fluid).

④ APP: "Atrophoderma of Pasini & Pierini":

- May represent very superficial or abortive form of Morphea. "More in Females"
- Paches Chi By:
  - Hyperpigmented, No lilac ring.
  - minimal induration
  - depressed border "cliff-drop" & well defined (sloping)
  - usually on Trunk Specially the Flexures & may follow the: Blaschko lines (Linear A. & Moulin)

- similar to Morphea in: clinical & hist. Similarity to regressing plaque of morphea (Atrophic Stage).

Path: epid. Hyperpigm. dermal Atrophy. Coll. Hyalinization & Clumping.

Severe S.C loss.

- 2 Conditions occurs at same pt.

good prognosis

- Not effective
- Spont. Resolution in (ms - ys)
- For Borrelia: oral Penicillin or Tetracycline (for 2-3 wk)

② Generalized Morphea:

- More Extensive & severe form of plaque Morphea (That) affect Large Area of skin

X But Without → sclerodactyly
→ Raynaud's
→ systemic affect

نزل عن SSC

- CIP: Start at the Trunk & rarely Extend to Acral Areas (Hand, Feet & Face)

(±) - May be ass. e:
- Dyspnoea: d.t chest involvement
- MS Atrophy.
- Anti-Histone Abs.

③ · Linear Morphea: (Linear Scleroderma) differ from plaque Type in:

· Age → Childhood (1st 2 decades).

· Serology: → high ANAs. (Homogeneous)

· depth: → deep dermis, SCT, muscle, bone ± meninges. (Fixed to underlying structures; Not as Morphea).

Variants

الأطراف

Linear Morphea of Limbs (LL>UL)

may be ass. ē:

① Spina bifida occulta.

② Faulty Limb development (Atrophy) & Joint Contracture.

③ Calcinosis Cutis

④ Melorheostasis: Cortical bone thickening

⑤ Concentric Rings around the limbs → Pseudoainhum.

ضربة بالسيف

en Coup de Sabre (Frontoparietal Morphea)

- Paramedian or Median depression or groove at Frontoparietal area of scalp.

· May extend:

· deep → event. meninges & brain.

· to scalp → Cic. Alopecia.

الوشم

Parry-Romberg Synd. (progressive Hemifacial Atrophy)

· Etiopathog. ?? Autoimmune, subtype of Morphea or d.t sympathectomy

· Epid. F>M, 5-15 ys.

① CNS: Trigeminal Neuralgia, Migraine & seizures.

② ocular: Enophthalmos, Horner Synd.

③ oral: delayed Eupt. of teeth, delatal Root Exposure & Resorption; difficulty in opening the mouth.

① Hemifacial Atrophy: severe Segmental (along Trigeminal) Morphea. differs from other Types in:

- Primarily start at deep de SCT ms & Bone
- No Sclerosis (WLS) (not L.
- Hyperpigmentation. Facial Hemiatrophy → Asyme.

② Alopecia

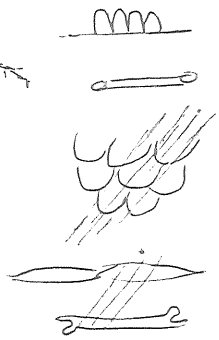
③ Epilepsy.

④ Enophthalmos.

4. Morphea profunda = disabiling Pansclerotic

- Morphea affect the S.C.T & underlying structures as the fascia. Most debilitating Type of Morphea.

- C/P: Indurated plaques c/c BY:
  - ill defined (Cuz it's S.C).
  - have cobblestone or pseudo cellulitte appearance. (or peau d'orange)
  - shows groove sign: depression along the course of vein, between ms. groups or both.



- may affect the entire Trunk or circumference of the limb. SCC may be a complicat°

Pathology of Morphea (Δ as pathogen

1. Vs changes: Endothelial swelling & Edema (Early stages at Lilac ring)
2. Autoimmunity or Infilt.: Retic. dermis & Trabeculae of S.C
3. Collagen degen. = Homogenizat° = Thick Coll., closely packed, Hypocellular & Mid-dermal "Trapping" of ECCrine gland (dermal-subcut junc°)

	Morphea	LSA.
Epid.	NL	(Thining of Rete) NL
DEJ	No Follicular plugging	Follicular plugging
Dermis	No Hydropic degen.	Hydropic degen. & subepid. bullae.
S.C.T	lower: Homogenized Collagen & mid-dermal ECCrine Trapping; Elastic fibs → NL; Inflamm.; Fibrosis	upper: Edematous Coll.; Absent Elastic (Elastic); No Inflamm. (mor) Fibrosis.

Morphea: Lat: Coll. Hyalin, ↑ extend.

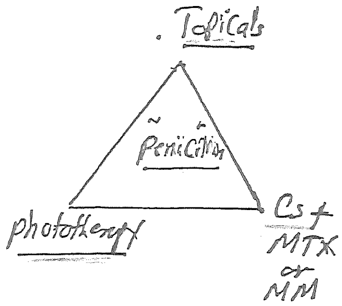
DD of Morphea 1- Morpheaform Condt°
2. SSc 3. Sclerodermoid Condit°

(JAAD CCR EMed 2012)

Treatment

فاكيه — Penicillin
- effective only during Active stage not Burnt-out Morphea

(لازم يستمر [illegible] وتقيم بعدها)



(A) Limited plaque Morphea

1st line — No response after 2 ms. → **2nd line**

1st line:
- Topicals:
  - Cs
  - ILCs
  - Calcineurin --
  - Daivobet (under-occlusion)
  - Aldara. (3-5 times/w)

Failed →

2nd line:
localized phototherapy. (UVA1, PUVA > UVB)

لو مفيش نتيجه بعد شهرين

(B) Generalized Morphea ēout Joint Contracture (3 lines)

phototherapy —8 ws Failed→ monthly Pulse Cs + Weekly MTX —Failed 2ms→ MM (Antifibrotic)

(C) linear at face or Joint Contracture

Pulse Cs + MTX —failed→ Add photo th. —Failed→ MM

- phototherapy:
  - UVA1
  - Bath PUVA (3mg/L psoralen لوضع الجزء المصاب لمدة ربع ساعة ثم ينتظر نصف ساعة ثم التعرض .. [illegible])
  - NBUVB
  - RePUVA

30 J/cm² for 36 Session
then stop (تتحسن بعد التوقف وليس في العلاج) except (linear)

Interface dermatitis (Diseases affecting DEJ = lichenoid Dermatoses)

Def.: inflammation of interface between epidermis and dermis (at DEJ), interface types:

1. Vacuolar type :

Interface dermatitis is dermatitis in which there is a degenerative change at the dermal–epidermal junction, with inflammation (mostly lymphocytes) mostly at the interface between the epidermis and dermis. *Liquefaction degeneration, vacuolar alteration* and *hydropic degeneration* are three synonyms for this degenerative change that occurs at the basal layer. Tiny vacuolar spaces appear at the dermal–epidermal junction, often leaving the junction indistinct (Eosinophilic blobs) at the basal layer and superficial dermis are called colloid bodies (dyskeratotic cells, hyaline bodies, Civatte bodies). They appear to represent altered collagen or basement membrane, fibrin and immunoglobulin, as well as degenerated keratinocytes. Melanin incontinence also frequently occurs in any interface dermatitis. Interface dermatitis may be divided into the *lichenoid type* and the *vacuolar type*, the latter having a less impressive inflammatory infiltrate.

- Dermatomyositis DM
- Drug eruptions (sometimes)
- Erythema dyschromicum perstans
- Erythema multiforme (sometimes) EM → prototype
- Graft-versus-host disease GVHD
- Interface dermatitis of HIV infection
- Lichen sclerosus LS
- Lupus erythematosus LE
- Secondary syphilis (sometimes) $
- Viral exanthems (sometimes)

EDP

- DM
- EM & EDP
- GVHD
- LS
- AIDS

- EM & EDP
- AICTDs & GVHD
- L. sclerosus

BCL

→ perivasc Ly

pig incontinence — Colloid bodies

2. Lichenoid type (lichenoid dermatitis) :

BCL

Lichenoid is defined by the pathologist as a *band-like infiltrate* of inflammatory cells in the superficial dermis. The band of inflammatory cells is usually mostly lymphocytes, except there may be plasma cells (syphilis, inflammation of mucous membranes, Zoon's balanitis) or eosinophils (lichenoid drug reaction). The clinician defines lichenoid differently to mean a papule or plaque resembling a lichen (symbiotic growth of algae and fungi) stuck on the skin. Some diseases that are lichenoid clinically are not lichenoid histologically (e.g. lichen simplex chronicus and lichen spinulosus). Lichen planus is both clinically lichenoid and pathologically lichenoid. Many of the diseases listed below that are histologically lichenoid are not clinically lichenoid.

- L.P
- Lichenoid DE
- L. striatus
- L. nitidus
- Lichenoid Keratosis
- Keratosis Lichenoides chronica
- pit. Lichenoides NCPLC
- $ → plasma Cell
- MF → Mg lymphocyte
- Zoon. Balanitis → plasma Cell

L.P & Lichenoid Dermatoses

- Called: Classical or Idiopathic L.C

(تعريف) Def. Diseases Resemble L.P Clinically &/or Histopathology

↓

See Classification at Interface Dermatitis

Lichen planus

- Def. Idiopathic, chronic Inflammatory dis. of (Skin / MM / Hair / Nails) Seen Most Commonly middle
- Pathophysiology:

CMI: Cell mediated immune Response of unknown origin that → damage of basal KCs that express altered self Antigens on their surface.

Some suggested Antigens that may ++ the CMI:

(I) Viruses: Sp.: HCV

(II) Vaccines: HBV Vaccines

(III) Bacteria: H. Pylori (not proved)

(IV) Contact allergens: amalgam, Copper & Gold

(V) Drugs: ACEInh. "ضغط"

(تعريف / تشخيص / علاج)

- May be ass. with:

(1) Liver diseases: HCV, HBV, BPC (cirrhosis)

(2) other Autoimmune dis.: LE, AA, Vitiligo.

(3) Anxiety & depression ± Risk Factor (عوامل)

Epidemiology

- Incid.: 1-4% of population.
- Sex & Race: equal
- Age: Any age can be affected but the commonest 30-60 Ys

LP

Classical L.P

Clinical Varieties

Classical L.P

Lesion Papules ± plaques:-

- Pruritic
- Polished
- Plentiful
- Purpule
- Planar (Flat Topped)
- Polygonal

→ 8 "Ps" of L.P

Show ← Koebner phenomen.
← Wickham's stride.

Site any

- Flexors of wrist.
- dorsal Hands → extensor
- Trunk
- Presacral area
- Medial thighs.
- Shins.
- Glans penis.

Healing → Chic **Hyperpigmentation**

- NB 1* **Wickham's Stride**

⊙ Gray White lace like Network, puncta or lines on the surface of lesions ∈ Can be seen after cleaning the surface of lesion with Oil & examination under **Lens**

it Represent: the **Hypergranulosis** seen in L.P"

2* **Color Changes** seen in L.P:

- initially → erythematous
- later (well developed lesion) → Violaceous
- Old (Resolving lesions) → Hyperpigmented.

Clinical Varieties

Varieties in **lesions**

- Linear
- Annular
- Hypertrophic
- Atrophic

Varieties in **sites**

- skin (classical)
  - face
  - Flexures
  - PP
  - Genital
- MM
- Hair
- Nails

- Ulcerative
- Bullous L.P.
- L.P & Bullae (pemphigoides)
- LE/LP overlap synd
- Acute Eruptive ✓ [onset ↵]

3 → Pruritus in L.P

- has a peculair finding in ā there is
  (10) scratch marks & Bloody Crusts because most patients react by rubbing rather than scratching.
- May precede the appearance of eruption i.e.
+ - it occurs in spasms & cause Frenzied itching that lasts for (minutes – hrs.) then gradually ↓

4 Course of L-p disease

- 50% → Resolve in 3ms.
  85% → " " 18ms.
- the following types tend to be more

Chronic:
- Hypertrophic
- Mucosal (<3% spont. resolution in av. 5yrs).
- Annular
- Large lesion
- childhood type.

Clinical Varities in lesions

⊙ Linear (Zostriform) (1-10%) may be d/t:
- isolated lesions arranged in lines
- (3) ↙ Koebner Phenomenon.
- Following Blaschko lines.

⊙ Annular lesions (10%)
- d/t either → Papules dry arranged in Annular pattern.
  → Papules & plaques Coalesce ē Central involution
  - Edge: Elevated, purpule – white.
  - Center: hyperpigmented.

NB. usually → affect: Glans & Flexures.
→ (non) itchy (rare)
→ Chronic.

Hypertrophic (L.p Verrucosus)

- usually at shins & around ankle (tibia)
- very itchy
- very chronic
- very dark post. inflamm. Hyperpigm.

aar → SCC may Arise

DD

(1) Resemble (PS) ?? How to diff ??

- PS
- LSC

- Violaceous
- Very Thick & itchy
- Symmetrical & NO any other PS. lesions.

(2) (LSC)

Atrophic

- usually represent Resolution of annular or Hypertrophic → (whites)
- Thinned-out plaques (resembling atrophic stage of Morphea or LSA).
- usually at Shins.

Ulcerative (Erosive): Rare on skin but Common on:

- MM → oral ulcerative L.p.
- ✓ scalp → CiC. Alopecia.
- Palm & soles → painful ulcers & Erosions
- Vulva + Vagina & Gingiva ⟷ "Vulvovaginal gingival synd"
- ✓ Flexual.

Vesicular or Vesiculobullous L.p

(2) clinical Varities

فرقين من (BP)

Vesiculobullous L.p

- Bullae affect L.p lesions only
- Seen in: Lower extremities & oral cavity → DIF-ve
- (d.t) Exaggerated subepid space caused by destruction of Basal KCs

- prognosis better than B.Pemphigoides → L.p & Bullae
- L.p Pemphegoides

. Elm. deposit. Bullae develop on Both L.p lesions & on NL skin. represent Coexistence of Both L.p & B.Pemphoid

C3 IgG at Roof of Bullae Not Base as BP

DIF+ve

L.p → ±L.p + B.P
Path & DIF → B.pemphigoides

L.p Erythematosus = LE/Lp overlap synd.

- unusual variant of L.p; ch by Discoid Lesions ē ↗ central atrophy, Hypopigm & Telangiecta
  ↘ periphery: Reddish-Purpule.
- usually at: dorsal Hands & Feet.
- (LE) - (±) ANA
- Path. & DIF: → Features (of) Both L.p & L.E.
- whether is it L.p (or) L.E ?? unknown
  ∴ search for other L.E manifs.

Dx by (DIF)

(L.p)
- Cytoid staining @ IgG, IgM, C3 at DEJ & intraepid. (+++)
- shaggy deposit of Fibrinogen (Typical of L.p)

(L.E) linear deposit

• Eruptive L.p (Acute L.p) = Exanthematous

pit. rosea

→ Widely & rapidly Generalized, dissiminated form of L.p:

— Course → self limited
→ hyperpigm. may resolve ēin (3-4 months).

• Variation in sites of Cut. L.p.

- Face
- Flexures
- pp.
- Genital.

---

asymptomatic

• Flexural L.p (Inverse L.p)

1. may be presented (ē) Classical L.p lesions (or) The Hyperpigm ± the sole manifs.
2. Similar to L.p pigmentosus.

clinical

L.p of The Face = (Actinic L.p = L.p Tropicus)

- ① affect sun Exposed areas e.g Face, dorsal Hands, V shapped area of Chest.
- ② Start at spring or summer.
- ③ Ch BY: Annular (Sometimes Reticulate or diffuse), Hyperpigmented (Blue gray), patches (Sometimes plaques) surrounded by tiny Hypopigm. papules
  - Type: With very mild or absent pruritus.
- ④ Pathology: as L.p + Spongiosis (a feature of dermatitis; so some authors Considered it as a variant of photoallergic derma or PMLE).

NB: 3 clinical Variants (see)

1. Classical Type (Dyschromic)
2. Melasma like
3. Granuloma Annulare like [annular]
4. Erythematous: Ass. E CAH (Erosive oral (L.P))

Palmo-plantar L.p

Wart ← Not as classical lesions of L.p But may be:

Wart: cryo, other lines ↑↑

1. Firm Papules & Nodules that are surrounded by Yellowish hue & may be ass. with spread Thickening of Palms & Soles (Tylosis).
2. ulcerative Variant ✓ may be ass. with Nail loss sp. Big Toe.

Non Itchy

Genital L.P

In:

- Male ♂
  - Commonest site: Glans Penis
  - Picture: (1) Classical papules, (2) annular pattern, or (3) linear whitish striae
- Female ♀
  - Site: Vulva, Vagina & Anus
  - Picture: (1) whitish macerated lesions (2) ulcerative

(50%) of ♀ ē oral L.P have undiagnosed Vulvar lesions [2006]

Pathology

(1) Hyperkeratosis (ortho) irreg.
(2) Hypergranulosis (wicket & irreg. Acanthosis
(3) Saw-toothed Rete < (pain-ful)
(4) Lichenoid tissue Reaction: → A: [Liquef. degen. BCL, Lichenoid infilt. Band like] / B: [Civatte Bodies (Apoptosis), Colloid Bodies, Pigment Incontinence (Melanophages), Max Joseph Spaces (intrabasal)]
(5) Flattening rete.

- DIF. "Λ"
  - (A) "Shaggy" deposit of Fibrin at DEJ
  - (B) "Granular" deposits of IgM
  - (C) Cytoid staining of IgG, C3, IgM at DEJ & st. Corneum

L.P of

- MM (Plasma Cell in infilt.) (NB)
- Hair
- Nails

Mucosal L.P

(سؤال امتحان)

(1) 3 sites.
(2) 5 associations.
(3) 8 Varities

- 3 sites:
  - Oral Cavity: Tongue / buccal mucosa / gingivae / palate
  - Genital: Vulvo Vaginal.
  - Others: Tympanic memb. / oesoph / Larynx / Bladder / anus.
- 5 associations:
  - HCV
  - DM
  - HTN
  - Mg (موضوع الدرس)
  - Autoimmune diseases: AA, Vitiligo, MG

(1) Also may associate Cut. L.p but (2) Low incid. < oral. → (Specially ulcerative) (Calc ± < CAH / PBC)

Clinical Varieties of Oral L.p

- Clinical Varieties:
  - Reticular (Commonest): whitish silvery lesions or papules in: Reticulate / Linear / annular or Lacelike. (Pattern)
  - Pigmented & White plaque like = Leukoplakia
  - Bullous.
  - Atrophic.
  - Erosive (Ulcerative) — discomfort & pain.
  - Desquamative: Chr. desquamative gingivitis.
  - Grinspan's Synd.

Incid. of Isolated oral L.p: 3%
7.3 (1) Reticular (2) Erosive (3) depressed Fixed white pla (Leuk. lik

Etiology of oral L.p

- Idiopathic
- Viral: (HCV) HPV, HHV6
- Contact Allergen → Tooth Pastes & Amalgam fillings.
- oral Lichenoid Drug Eruption — Gold / NSAIDs, Antibio.
- Part of GVHD
- Mechanical Trauma.

M(F) 1:4
30–70 Ys
ass. c. Cut & Mucosa in ≥ 50%

Q → **L.p of the Hair** (Follicular L.p = lichen planopilaris) (Lpp)

4 Varieties:
1. Multiple Follicular Keratotic plug sym. by Violaceous rim.
2. Scarring Alopecia & Pseudo pelade of Brocq
3. Graham Little Piccardi-Lassueur syndrom

Triad of:
- Cic. Alopecia of scalp
- non Cic. Alopecia of axillae & groin
- Follicular L.p of Body, scalp or Both.

4. **Frontal Fibrosing Alopecia** (thought to be L.p variety)
   - unknown cause
   - ± L.p.
   - progressive.
   - post menopausal >50 y.
   - loss of hair of Front & side of scalp
   - skin ± NL / pale or mildly scarred with Peri follicular redness.

L.P of The Nail

Pterygium
↳ Pterygium
↳ 2o Nail

Varieties:

d.t matrix affection →
- Lat. thining
- Longitudinal ridging – Melanonychia
- Fissuring
- dorsal pterygium → Pterygium

d.t Nail bed affection →
- Yellow discoloration.
- Sub ungual Hyperkeratosis.
- onycholysis

◎ Twenty Nail dystrophy syndrome: may occur in children > Adults.

(1) Q: What is Pterygium ??

- Pterygium = Greek word means "Wing" Pterygium w is classically Ass. ē L.P
- Mechanism of its formation: L.P attacks the matrix (Nail forming unit) → permenant destruction & scarring → failure of growth of Nail plate at This site → The proximal Nail fold becomes attached to the Nail bed directly & both grow distally → "Wing" like appearance.

NB
- Pterygium
  - dorsal: L.P, SJS.
  - Ventral: Sclero-derma

- Pterygium inversus Ungium: → (Scleroderma) Failure of Separat bet! distal end of Nail Plate & The underlying distal end of The Nail bed.

(2) Q: Twenty Nail dystrophy synd (Trachyonychia) (Rough)

- Condition Ch BY Progressive Nails affection Call nail dystrophy (or mat Nails) w shows (ridging & pitting & Loss of Luster & roughness)
- Usually: at Child hood (10-20%) 20-25% → ± improved
- AE: unknown but ± d.t:
  (1) L.P (2) Psoriasis (3) Eczema (4) Alopecia A. (5) Autosomal dominant (AD) (6) ...

Lichenoid Drug Eruptions

أم أجرا لازم Q

1. Cut. LDE
2. oral LDE (Lichenoid CD)

أدوية تتخرج العلاج في نفس الوقت تعمل LDE ??
- Griseofulvin
- Flagyl
- Retinoids
- Anti-malarial
- Sulfa.

- **These Drugs causes**: L.P like lesions (clinically & pathologically)

Lichenoid Drug eruption → "هام جدا"

دا ليسيري

- أدوية كثيرة جدا (دراسة 2 . 12 جدول) (وكلها شهيرة)

Gold is the commonest.
Pattern (1) PR, Eczema, PS.
(2) Bullous (3) ulcerative
(4) oral (5) pigmented...
(6) Pemphigoides
(7) Erythrod.

1. Anti HTN
   - ACEI.
   - BB.
   - Methyldopa.
2. Antimalarials.
3. Diuretics (Chlor & Hydrochlor thiazides)
4. Gold
5. Quinidine.

(ركز كويس) **lichenoid Drug Eruption** ??

(قوي جدا)

LDE:
زي الجلد بس يغير الصفات
بـ (ms - we)

Lichenoid CD
- ✱ oral LDE
- Amalgam, Gold, Mercury, Tooth pastes.
- C/P as oral L.P

More:
- **Skin**
  - Generalized (sparing classical Lp sites), larger scaly, itchy, Hyperpigm ↑↑
  - Eczema, PS. or Pit. Rosea like (Frequently) photo distributed. (No Wikham's). No hypergranulosis
- **No**
  - **Hair** → severe falling.
  - **MM** → usually spared → (except dental (الطعم الأسنان) - amalgam Fillings - Gold - Mercury)
- **E**
  - **Blood**: Eosinophilia
  - **Biopsy**
    - Eosinophilic infilt.
    - Parakeratosis لا
    - Focal interrupt. of granular layer.
    - Cytoid bodies in st. Corneum & granular layer (rare in Lp)
- **H.x** of Drug intake
- **on stop** of drugs → Resolution / Gold chelators (BAL or EDTA)

14 | **diuretics** → persistant ulceration of Lower Lip

EDP = Ashy dermatosis

- Slowly progressive appearance of gray / gray-blue / gray-brown oval shapped macules & patches at trunk & proximal extremities ē their axis // to Ribs (as pit. Rosea) (Follow langers lines)
- occasionally: may be surr. by peripheral rim of Raised Erythema (may be absent or appear then disappear)

Rim of Raised Erythema

- Clinically: Spare Palms, Soles, mm, Scalp & Nails.
- Prognosis: Children: spont. Resolution: ≃ 7o% ē in 2-3 ys
  Adult: more chronic.
- Histopathology: Center of lesion: Post inflammatory Hyperpigm.
  Raised border: Lichenoid React°.
- Treatment: 1. Clofazimine for 3-8 ms
  2. Laser: for dermal Melanin
  - in children: spont. Resolut° in 7o% ē in 2-3 y.
  - Adult → persistent.

NB
- Age ↓c
- oral shape ↓c
- Arrangement along langers ↓c
- elevated age ±
- distribut°: Neck, Trunk & extremit.

IEMP ± variant

Lichen Pigmentosus

DD from Achnic
- No classical lesions
- affect sun-protected areas.

Variant of L.P (Ch By)

- Affect darker skin individuals III & IV
- Severe hyperpigmentation specially Face / Neck (Face & Flexure)
- May be ass. ē prurituss & L.P lesions elsewhere.
- This type may Represent the usually L.P that Resolve ē marked Hyperpigm. (probably d.t the Racial back: ground).

darker skin
Face & Flexure
s. ē

DD EDP: dark skin ↔ Late onset (40-50) Facial & Flexure

Treatment of L.P (Self Limited ~in 8-18 ms)

Topical (4)

1. Cs
   - Superpotent topical 25gm/w
   - Intralesional
   (For oral L.P & Hypertrophic L.P)
2. Calcineurine inhibitors (Topical) CI (للتقشر)
   - Tacrolimus 0.1% oint
   - Pimecrolimus cream.
3. Cyclosporine (Topical) for ulcerative oral.
4. Retin A Cream (oral L.P).

Systemic (10)

1. Cs
2. MTx
3. Dapsone
4. Cyclosporine
5. Thalidomide
6. Sulfasalazine
7. Mycophenolate Mofetil.
8. Biological
   - Basiliximab
   - Alefacept
   - Efalizumab
   → IL2
9. Antimalarial
10. Griseofulvin
    - Metronidazole
    - Low molecular weight Heparine (LMWH)
11. Retinoids

Phototherapy

- UVA1
- PUVA
- NB-UVB
- Excimer Laser
- ECP

NB on the

* **Topical:**
  - Cs: for oral L.P → use Kenalog in Oral base (كينالوج في قاعدة فموية)
  - Calcineurine: use for in oral L.P & Vulvar lesions (but may ↑ Risk of Mg)
  - Tacrolimus 0.1% oint أقوى → Pimecrolimus.

Systemic ttt

Apremilast PDE4 inhibitor used for ttt of Ps, Rh. arthritis & ank. spondylitis

⊙ Cs: indications of systemic Cs

1- Skin L.P < Severe or Acute generalized

2- MM → ulcerative oral L.P

3- Hair → Progressive scarring L.P (Graham little synd)

4- Nail → Progressive Nail affection.

(جرعة) prednisolone: 5-20 mg/d for 6 ws then gradual withdrawal over 6 ws. (Higher doses are needed in oral Erosive)

لو كان عنده مشاكل في الكبد أو الكلى

⊙ Retinoids: Acitretin: 30 mg/d for 8 ws. (but) " أمر جزئي أول الخطوط "

⊙ MTX: low weekly dose.

⊙ Cyclosporine: for Resistant cases for < Cs & Retinoids
useful to ↓↓ progression in Graham Little synd

⊙ Griseofulvin tab: . مرتين ٣-٦ شهور { ٢ قرص صباحا ٢ قرص مساء } (جرعة أدوية)
↳ Imperical ttt
→ good Result (but still not universally accepted)
→ useful in ulcerative oral L.p

(oral ulcerative + Erosive) — الأفضل

⊙ Metronidazole tab: ٥٠٠ مجم مرتين يوميا لمدة ١-٢ شهر
Immunomodulating effect → very good Response ē Generalized L.P (generalized) — الأفضل

⊙ Low Molecular Weight Heparin: (3 mg/W, S.C) "شركة للعلاج"

⊙ Hydroxychloroquine → Excellent ē oral L.P. (رأي أندرز)

Graft Versus Host disease or Reaction (GVHD)

def Condition That may occur Following Transplantation in which the donor's Immune Cells in the Transplant (graft) make Antibodies Against the patient Tissues (Host) → Attacking The vital organs.

Clp
- Skin → Rash
- GIT → diarrhea
- Liver → Jaundice.

Incid.
1. Usually following: Hematopoietic Stem Cell Transplant (HSCT) (90%) → BM
2. less Common: Solid organ Transplant, Blood Transfusion → Non irradiated To Immunodeficient / immunocompromised / Mother-to Immunosuppressed Neonate

Types of GVHR

Acute (< 100 ds) (usually 4-6 wks)
- occurs in < 3 ms from Transplantation
- **A. Skin**
  - 1st: Acral Rash (Face, Hands & Feet)
  - Then: Generalized maculopapular (Morbilliform) & ± TEN like & perifollic. Accentuate.
  - (i) Morbilliform. (ii) Erythroderma. (iii) TEN like.
- **Staging**
  - I: Rash < 25% BSA
  - II: " 25%-50% "
  - III: " 50-100% " (Erythroderma)
  - IV: Erythroderma & ± bullae / TEN like.

Chronic (> 100 ds)
- occurs after > 3 ms from Transplantation
- usually evolves from acute but may occur denovo
- **Skin:**
  - Early → Lichenoid
  - Later → Sclerodermoid
    - LS
    - Morphea form
    - Eosinophilic Fasciitis

Both types → predispose to skin inf. & Sepsis.

B. GIT → Watery ± Bloody diarrhea & stomach Cramps.

C. Liver → Jaundice & Abnl LFTs.

3 Mucosa → GIT, liver, eye:
- Mucosa: Eye (KCs), Salivary (Sicca), Bronchiolitis
- Exocrine dysf → GIT, pancreas

Mx
1. Hospitalization
2. Immunosuppressives: Cs, MTX, Cyclosporine & Tacrolimus

(GVHD) طعم ضد عائل

- MR — Acute : 75٪
  Chr. : 10٪

Clinical staging and histologic grading of acute graft-versus-host disease.

CLINICAL STAGING AND HISTOLOGIC GRADING OF ACUTE GRAFT-VERSUS-HOST DISEASE

	Clinical			Histologic		
Stage	Skin rash	Liver bilirubin	Intestinal tract diarrhea	Grade		
1	<25% BSA	2–3 mg%	500–1000 ml/day	I	Focal or diffuse vacuolar change	→ Vacuol. degen.
2	25–50% BSA	3–6 mg%	1000–1500 ml/day	II	Grade I features + necrosis of keratinocytes and lymphocytes	← Necrosis
3	>50% of BSA – Generalised erythroderma	6–15 mg%	1500–2000 ml/day	III	Grade II features + focal DEJ separation with formation of vesicles	← Vesicles
4	Generalized erythroderma with bulla formation TEN	>15 mg%	Diarrhea, >2000 ml/day Severe abdominal pain, with or without ileus ±	IV	Grade III features + formation of bullae	← Bulae.

HL

Risk of GVHD

(1) Donor
- ♀, Elderly, HLA incompatab.
- Unrelated reciepient
- Male recipient from ♀

Reciep
- Elderly

3 Stem Cell Source:
PBC > BM > Cord Blood.

4. More intensive Myeloablat (→ AGVHD) & less aggressive Immunosuppr

• DD of AGVHD

1. Drug Eruptⁿ & Viral Eruptⁿ.
2. Engraftment Synd:
   - Non specific, in 2 ws
   - Fever, Rash, Pulm. Ed.
3. Toxic Erythema of Chemo Therapy: Specially if PP. or Intertrigenous

•• Ht of Cut Manifest:-

1. Combined ē Immunosuppressives:
2. Topical Cs (mild dis)
3. Phototherapy
4. Sun-protect.

Mechanism

1. AGVHD
   - ++ Host APCs
   - ++ Donor Tcs
2. CGVHD
   - Auto abs product
   - Cutᵉ Sclerosis.

•• Other Mucocut. Manifs

- Lupus or OM like & SS Photosensitive Eruptⁿ
- Xerosis & Ichthyosis
- Leopard like pigm. & vitiligo ∩ depigm.
- KP & poikilod.
- orogenital ulcerat
- Angiomatoid papules
- Hemolytic An.
- Pulm. fibrosis

HI

- Prophylactic:
  - Ciclosporine
  - MTX +
  - Anti-CD52 (Alemtuzumab)
- Active
  - Cs or
  - others
    - MM
    - Sirolimus
    - Anti-IL2R (daclizumab)

Ht of Skin
- FDA in prevent
- IVIG ✗

16

Lichen sclerosus

(or Lichen sclerosus et atrophicus)

Def. → Chr. inflammatory disorder that affect the skin & mucous memb. & Encompassing 3 disorders:

- skin → 1- Lichen sclerosus et atrophicus (LS
- vulva → 2- Kraurosis Vulvae
- glans → 3- Balanitis Xerotica obliterans (BXO)

Epidemiology: ♀ > ♀ (6:1)

- Age: female late → 2 Peaks → Prepubertal (8-13)
  Postmenopausal (50-60

AET: unknown but ± d.t: (as)

1- **Trauma:** evidence
- May act as ppt. Factor e.g Vaccinat & surgic scar.
- Circumcision → improve it

Pathophysiology
- Inflamm. & altered fibroblast funct → Fibrosis in consider it variant of SCL.

2 **Infection:** Borrelia Burgdorgeri may play a role (±)

3 **Autoimmune:** • presence of organ specific Abs (Anti glyco-Protein ECM-1) & Concomitant occurance of other autoimmune diseases.
(2004) → ass. ē Histologic evidence of vasculitis → reduplicat of BM.

5 **Ischemia & Hypoxia** → ↑ glut-1 & ↓ VEGF expression in affected skin.

4 **Endocrinal:** Evidence
- higher in ♀s
- high Incid. Postmenopausal & prepubert
- Association Menarche

• L.S

- Genital (85%)
  - Male
    - Balanitis Xerotica obliterans (BXO)
  - Female
    - Kraurosis vulvae
- Extragenital (15%)
  1. Cutaneous
     - A – Usually asymptomatic so
     - B – May be left untreated.
  2. Oral MM
     - Resemble L.P
     - Rare
     - Usually : sec ē generalize L.S

Oral L.S كتير من حالات ال
L.P تم تشخيصها خطأ على أنها

Cut. Lichen sclerosus

(LSEA)

CIP :

- Early stage : papules & plaques (Ch^By) Guttate – large

شبه Vitiligo

لونها – White
عددها – Polygonal
شكلها – Flat-topped (بالتساوي)

Site: Any but commonest is back / shoulder ... (كتاف)

- فيها – Show : evenly spaced dells or Comedolike Plugs (Correspond to obliterated appendageal ostia) & Telangiectasia. (dells or com., Telang.) (or dilated)
- حواليها – surrounded by Erythematous – Violaceous halo.
- حجمها – Size : Few millimeters (LW like = Guttate) (Lwith dus / كتير) to Large plaques (Entire back like).

- Late (Atrophic) stage:
  - plugs & dells disappears → white, soft, smooth, wrinkled, Porcelain white plaques.

Symptoms: usually ... (Itching)

Genital L.S

(Adults > Children)

SCC

Male

Balanitis Xerotica obliterans

Sites:

- Commonest → glans & prepuce (inner Aspect)
- Rare: → shaft, scrotum & perineal.

- lesions:
  - Early: → Post Traumatic, Hgic like lesions (bluish Erythema atrio)
  - Late: white, Atrophic, Sclerotic Plaques.
    - → Constriction:
      - phimosis → Failure of retraction of prepuce
      - paraphimosis → ~ ~ Repositioning ~ after retraction
      - Painful Erect⁻ (Dyspareunia)
      - dysuria
      - urinary obst.
      - → SCC

NB
- It is more Common in UnCircumCised
- Koebner phenomenon: may be present in L.S.

Female

Kraurosis Vulvae

- Site: usually Vulva & Perianal & then ↑ surface other areas e.g Labiae, & Cilums.
- Lesion:
  - Early → as in men (but more bluish erythematous Common); bullae may occur (DD Sexual Abuse)
  - Late: as in men
    - Perivaginal & Perianal encircling lesions are Common
    - → "Figure of 8" / Hour glass or butterfly like.
    - Clitoral & Labial affect⁻ & obliterat⁻ is Common.

- Symptoms:
  - Itching
  - Fissuring (3)
  - Erosions
  - dysuria
  - dyspareunia (3)
  - discharge
  - loss (2) → Labia minora, clitoris, urethral meatus
  - Leukoplakia (Sol.) → ± SCC

Prognosis ✓

- Acute genital lesions → good.
- Chr. (genital) & Extra genital: → Poor.

Histopathology:-

1. Hyperkeratosis with Follicular (in non Mucosal) plugging [Compact orthokeratosis]
2. Atrophy of St. Malpighii
3. Hydropic degeneration of basal cells (BCL). (Vacuolar Type Int. I.D)
4. upper dermis: marked Edema & (Homogenization) of Collagen → sclerosis
5. Mid dermis: → Inflammatory infiltrate (deep band like).

if +ve Sq. Hyperplasia → ± SCC.

DD: Cut. lesions:

- Morphea.
- Atrophic L.p.

Genital lesions:

- Genital L.p
- LSC
- VIN
- Extramammary Pagets. (EMPD)
- Pemphigoid of MM.

Treatment of LS

CS → Antiinflam immunosupp (lymphocytes)

Clearance phase (6-12 ws) Super potent or ILCs + Tacrolimus

Maint. phase

Topical:

- Cs: Topical & IL (Superpotent)
- Tacrolimus
- Tretinoin
- Calcipotriol
- Emollients.

- ♂ → Circumcision improves it
- ♀ → (No) excision except if (SCC)
- Potaba - PDT

Cut:

- Reassurance → (No) ... Fertility
- Symptomatic.
- Potaba
- PUVA, UVA
- Acitretin
- Antimalarial.
- PDT

Potassium - Aminobenzoate = potaba

- one of (Vit B) Members
- Mechanism: Antifibratic & Anti-inflammatory.
  - ↑ Tissue O2 level → ↑ MAO level → -- fibrosis.
- Dose: 12 gm/d (Capsule Potaba = 0.5gm) → divided over 4 doses → gradually to 24 gm/d.
  (with meals)
- SE:
  - GIT Upset
  - Rash
  - Hypotension (↓BP)
  - Leukopenia.
- C.I:
  - sulfonamides
  - Hypoglycemia
  - Renal-dis.

NB: Topical Testosterone is (no) More effective than Emollient & in one trial was worse than Emolients as maintenance after clearing ē Cs

NB → Emollient > Topical T

Lichen Nitidus (L.N)

* **Def:** rare, chr., skin Eruption ch' by Eruption of Micropapules (Pin head sized) → Asympt, Skin Colored, Flat Topped — usually affect → Children & Young Adults.

* **Aet:** unKnown; Controversy Coexist bet. relation of L.P & L-N (Both may Coexist)

* **Epid:**
  - Sex: M = F
  - Age: any but Commonest → Children, Early Adulthood

* **CIP:**

Micropapules (1-3 mm) (Pin head sized) (Tend To cluster)
- Asympt → C/out (±) Pruritus) Hypo ≃
- Skin Colored (shiny) → (±) (Hyperpigm in Blacks)
- Flat topped → (±) ē Central depression)
- Polygonal or Round → (±) ē Pink-blu-Yellow hue)

- **Show** → Koebner phenomenon → linear Pattern
- **Site:** L.N: may affect:
  - **A. Skin:**
    - Commonest → Trunk (Chest & Abd), Flexor of Upper Extremities, dorsal Hands, genitalia
    - lessCommon: Face, PP., Lower limbs.
  - less → **B. MM** → White papules (or) plaques
  - less → **C. Nail** → Pitting, ridging, splitting & linear striation. & ± Perungual Lesions.

Clinical Varieties: [localized / Generalized] [linear / Actinic] [Perforating / Vesicular / purpuric / Agic / Keratodermic] 23

Prognosis: Spontaneous Resolution occurs in 2/3 of Cases ē in ≤ 1 y.

HP: 1- Lichenoid ID
2. Infilt. is → Granulomatous
→ Huged by downward prolif. of Rete Ridges (Rete Ridges) "Clutched of infiltrat (2-3 DP width)" ; Ball & Claw configuration

DD: [. Lp
. Frictional lichenoid dermatitis (Elbow & knee)
. papular ECZ.]
[Papular Sarcoidosis.
. L.p
. lichen-scrofulosorum.]

سؤال امتحان

	Lp	Lichen-nitidus.
Lesion:	. Itchy . Violaceous . pinhead-large sized . PI. Hyperpigm.	. Asympt. . skin-Colored . Pinhead sized. . Commonly PI. Hypopigm.
MM Hair Nails Wickham Striae	+ve	. Rare - Absent. ✗
HP	لا يهم	لا يهم
TTT	لا يهم	

→ Reassurance (Self limiting)
. Antihistamines
. Cs . phototherapy . Acit.
Imperical ttt → Itraconazole.

Lichen Striatus

- **Def** Asymptomatic, self limiting, linear dermatosis primarily affect children. (5-15 ys)

- **Epid.**
  - M : (F) = 1:2-4
  - Age : [5 - 15 Ys] (rare in infants & Adults)
    عادي

- **Etiology** ?? Genetic, Enviromental, (AD) Autoimmune & viral.

- **C/P** → (skin) / (Nail)
  - (skin): Early stage & Late post-inflamm. stage.
    1. → Band of Papules (± Vesicles); Scaly, Skin Colored - Erythematous Continous or Interrupted.
       - usally at Single at (L.L) but (±) → Bilat / at Blaschko / at Any site.
       - ممكن يبدأ بـ Trunk ← وينزل لحد Limb
       - → [Self limiting] ē in 3 - 12 ms → PI. Hypopigm.
    2. → linear (or) Blaschkoid Hypopigmented Streak [(±) the 1st presentation] أوقات
  - ممكن يجي بعد أو أثناء الجلد → [Nail]: ridging, splitting, subung. Hyperk. (onycholysis, dystrophy usually affect the* (lat) edge of one Nail.

- **Investigations**
  1. **Dermoscopic** :-
     - White structures: Well defined, deep white resembling Wickham striae.
     - Brown structures: Brown, Keratotic, Cribriform ē red dots surr. by Pale Halo.
  2. Feature of (ECZ + L.P) ← **[HP]**: lichenoid Type ID; infilt. ch. by (±) Granulomatous; Concentrated around (HF), (Sweat glands)
     - Epid: Spongiosis, Dysk, Parak.

Linear lesions :-

- VEN
- ILVEN
- Nevoid ps. (linear ps).
- Blaschkitis. (Multiple lines, Trunk, Eczematous)
- Linear: L.P, Darier (HP), GVHD.
- Basal Cell Nevus Synd.
- Basaloid Follicular Hamartoma
- linear porokeratosis (HP)

متشابهين جداً

TTT :-

- Reassurance (Self limiting ein 3-12m)
- Topical Cs
- Emollients
- Pimecrolimus
- Cs + Retinoids

A. Lichen Striatus (Vs) Linear L.P

- Asympt., Erythematous → leave → PI Hypopigm
- Severely itchy, Violaceous → leave → PI. Hyperpigm.

B. VEN (Vs) ILVEN

VEN:
- No Erythema
- No itching
- at birth or Infancy.

ILVEN:
- Erythema
- Marked Itching
- Infancy or childhood.

C. ILVEN (Vs) Linear (Nevoid) PS

ILVEN:
- Early onset/Slowly progressive
- Severely itchy
- (-Ve) Auspitz
- Resistant to ##
- (HP) Psoriasiform + alternating bands of Hypergranulosis (ē) overlying orthokeratosis (&) Agranulosis (ē) parakeratotic Hypergranulosis.
- Immunohistoch: ↑ K10, ↓ T Cell Subsetance
- Criteria for ... (illegible)
- (No) post inflam hypopig

Linear (Nevoid) PS:
- Late, Slowly Prog.
- Asympt.
- +Ve Auspitz
- Responsive (Sp → Anthralin & Anti TNF).
- (HP) → معروف (Ps)
- dermovit under occlusion 3w → dramatic Response
- → (No) itching.

وجه مقارنة

١) كانوا اعتبروهم نفس المرض.
٢) وجود حالات للمرضين معاً
٣) التفسير: تجاور الكيانات
٤) حالات مرضين مختلفين

Keratosis Lichenoides Chronica

(Nekam's disease)

→ (Rare) Cut. dis start at birth or adulthood (20-40ys)
& ch By:

1. Violaceous Keratotic Lichenoid Papules
   - Linear & Reticulate or
   - Symmetrical distributed on limbs &
   - Asymptomatic (~~OO~~ L.P) Trunk.
2. S.D. or Rosacea like or psoriasiform Eruption on upper Portion of (Face)
3. Hoarseness of voice & Nail changes, oral ulcers (50%)
4. PPK.

- Course: usually Chronic & may regress (lesions) with Summer & with Aging.
- Histopath: → very similar To (L.P) (may be Considered as a variant of L.P).
- Treatment (symptomatic & unsatisfactory):
  - Cs
  - MTX
  - Cyclosporine
  - Etretinate / ACit. & PUVA or RePUVA
  - Vit A
  - PUVA

DD. HP For (L.P)

- Parakeratosis
- Atrophy of st. Malpighii.

Non itchy L.p

- Annular L.p
- oral
- Hair
- MM
- Nail
- Palmoplanter (pp)
- Actinic L.p